Strategies to improve myocardial reperfusion after primacy PCI : the value of pharmacological interventions and thrombus aspiration

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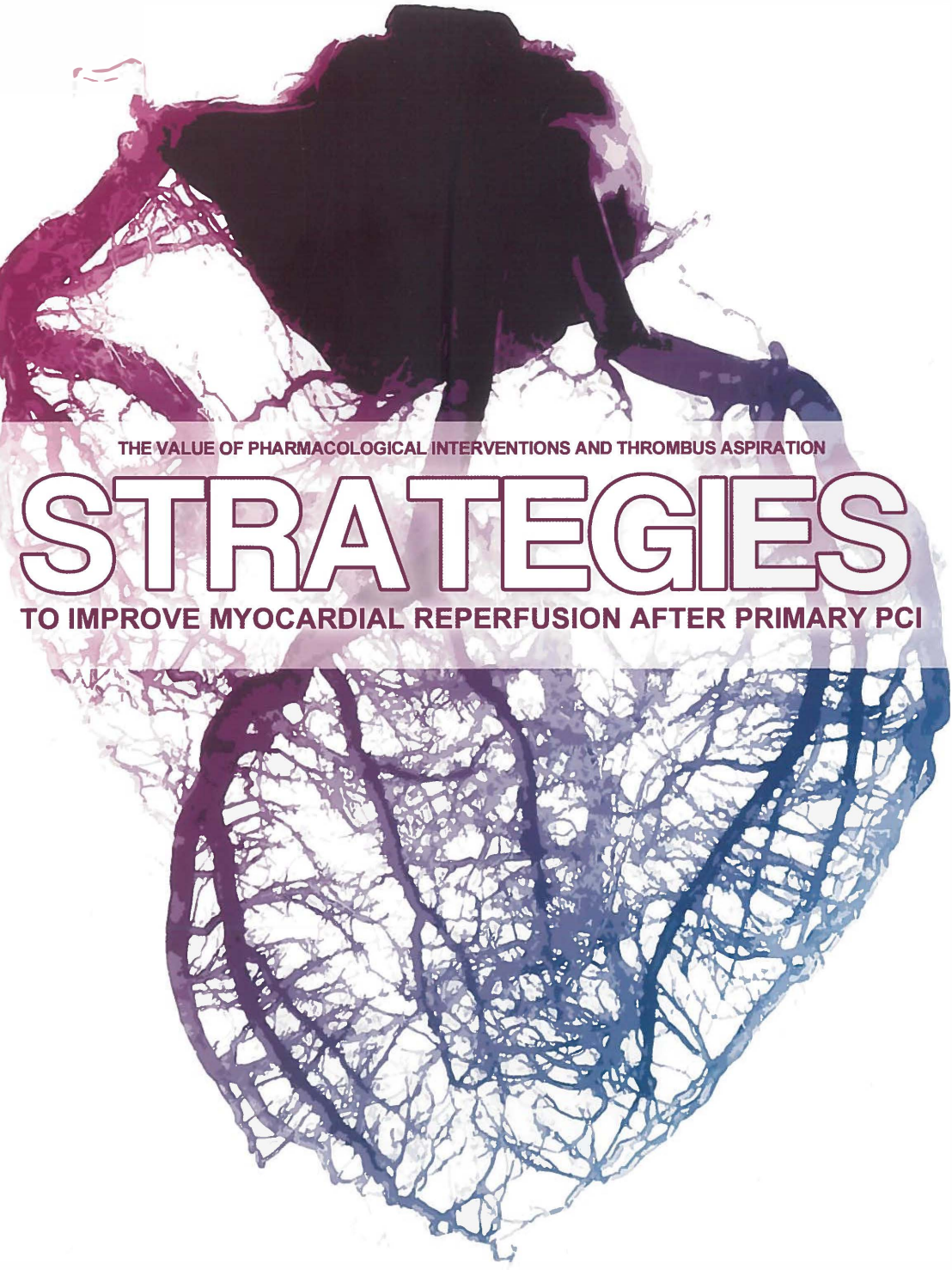

THE VALUE OF PHARMACOLOGICAL INTERVENTIONS AND THROMBUS ASPIRATION

STRATEGIES

TO IMPROVE MYOCARDIAL REPERFUSION AFTER PRIMARY PCI

Pieter-Jan Vlaar

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The value of pharmacological interventions and thrombus aspiration

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Stellingen behorend bij het proefschrift

Strategies to improve myocardial reperfusion after primary PCI

The value of pharmacological interventions and thrombus aspiration

1. Het routinematig gebruik van medicijn-afgevende stents bij patiënten met een ST-elevatie myocardinfarct moet worden afgeraden. (dit proefschrift)

2. Na de diagnosestelling van een ST-elevatie myocardinfarct moet zo spoedig mogelijk een oplaaddosis clopidogrel gegeven worden. (dit proefschrift)

3. In het geval van meervatslijden dient de primaire PCI beperkt te blijven tot het aan het infarct gerelateerde vat. (dit proefschrift)

4. Het gebruik van trombus aspiratie leidt in vergelijking met conventionele PCI tot een verbeterde myocard reperfusie en klinische uitkomst bij patiënten met een ST-elevatie myocardinfarct. (dit proefschrift)

5. Trombus aspiratie is ook bij de meeste patiënten met een non-ST-elevatie myocardinfarct toepasbaar en veilig. (dit proefschrift)

6. Een valide vergelijking tussen zorgverleners is op basis van de huidige kwaliteitsevaluaties niet mogelijk.

7. Het verschil in werkzaamheid tussen merk- en generieke geneesmiddelen is voornamelijk gebaseerd op het placebo-effect.

8. Onderzoeksafdelingen afrekenen op impactfactoren leidt tot een grotere publicatie bias.

9. Het tijdig omkeren op een verkeerd ingeslagen weg kan zowel in de bergsport als in de geneeskunde veel gevaarlijke situaties voorkomen.

Pieter-Jan Vlaar, Groningen, 20 april 2011

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Strategies to improve myocardial reperfusion after primary PCI

The value of pharmacological interventions and thrombus aspiration

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CHAPTER 1

General introduction and scope of the thesis

Acute myocardial infarction is a leading cause of death in adults in North America and Europe.[1,2] Coronary plaque fissuring or rupture is the initial event of acute myocardial infarction leading subsequently to exposure of the underlying subendothelial matrix, activation of platelets, thrombin generation, and thrombus formation.[3,4] An occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI).

The goal of treatment of patients with STEMI is to achieve rapid epicardial and myocardial reperfusion and to maintain this initial result at follow-up.[5] There are two methods of treatment to re-open an occluded artery: administering a thrombolytic agent and percutaneous coronary intervention (PCI). In the 1990s and the beginning of the 2000s, many randomized controlled trials have shown that PCI for STEMI is associated with improved outcome compared to thrombolytic therapy.[5-7]

Primary PCI involves dilatation of an acutely occluded coronary lesion, thereby restoring epicardial blood flow to the myocardium. This dilatation, however, also causes compression, fracturing and fissuring of the plaque and thrombus load. This accounts for some of the major complications (e.g. restenosis, (sub)acute closure, distal embolisation) associated with PCI, resulting in impaired epicardial and microvascular reperfusion.[8-15] The aim of this thesis is to explore new strategies to reduce these PCI-related complications, and to improve epicardial and microvascular reperfusion after primary PCI.

Part I Impaired epicardial reperfusion

Restenosis

A major limitation of PCI is the occurrence of restenosis, which occurs in 20-50% of patients treated with balloon angioplasty alone within the first months after a successful intervention.[13-16] Restenosis is the arterial healing response seen after vascular injury caused by balloon dilatation. It is based on three processes; elastic recoil immediately after balloon dilatation, late vascular contraction (remodeling) and neointimal proliferation due to vascular injury.[13,14] The implantation of coronary stents during PCI prohibits almost all elastic recoil and late vascular contraction of the dilated artery. However, stent implantation is unable to inhibit neointimal formation, but even enhances it, resulting in so-called in-stent restenosis. The incidence of in-stent restenosis ranges between between 10-30%.[15-18] Drug-eluting stents (DES) have become the main approach to avoid in-stent restenosis. These stents are coated with anti-proliferative drugs and have shown to reduce the amount of in-stent neointimal hyperplasia compared to non-coated stents (bare metal stents, BMS).[19-21]

In 2003 DES received expedited approval for clinical use based on the results of initial prospective randomized controlled trials enrolling mainly stable patients with discrete coronary lesions.[22,23] Rapidly thereafter DES were also routinely used for off-label indications, such as STEMI.[24,25]

Because of the fact that patients with STEMI have been categorically excluded from most of these trials, it remained unclear whether the experience with DES in stable patients could also be extrapolated to patients with STEMI. In Chapter 2 the safety and efficacy of DES vs. BMS in patients undergoing primary PCI for STEMI is investigated and discussed.

Thrombotic complications

The enhanced thrombotic environment of STEMI contributes to a higher risk of thrombotic complications during and after primary PCI.[4] The combination of acetylsalicylic acid and an ADP-receptor inhibitor (dual antiplatelet therapy) is currently the optimal medical strategy to reduce this risk of thrombotic complications.[5] For patients undergoing PCI for stable angina or acute coronary syndromes, several studies demonstrated that starting dual antiplatelet therapy before PCI (pretreatment) was associated with a further reduction of thrombotic complications compared to starting after the PCI.[26-31] In patients treated with thrombolytic therapy, additional administration of the ADP-receptor inhibitor clopidogrel was associated with a higher incidence of early epicardial patency and improved clinical outcome.[32] Based on these findings, dual antiplatelet therapy is often started on site by ambulance or emergency department staff directly after electrocardiographic confirmation of a STEMI.[33] Early administration of these agents may induce early epicardial flow, more complete platelet inhibition and improve outcome after primary PCI for STEMI. Although no randomized data have been published on the impact of pretreatment with clopidogrel in the setting of primary PCI for STEMI, it is widely used in routine clinical practise. To evaluate the impact of clopidogrel on early reperfusion and clinical outcome, a systematic review was performed, of which the results are presented in chapter 3.

Multivessel disease

The majority of the patients presenting with STEMI have extensive coronary artery disease. As a consequence 40-60% of the patients have, besides the culprit vessel lesion, also one or more significant non-culprit vessel lesions.[34-35] After treating the culprit vessel, significant lesions in non-culprit vessels suitable for PCI can be treated according to 3 different strategies; (1) conservatively, (2) directly by means of a multivessel PCI or (3) during staged PCI procedures. Current guidelines discourage treatment of non-culprit vessel lesions in hemodynamic stable patients, mainly because of a possible increased risk of complications when performing PCI in the enhanced thrombotic and inflammatory environment of STEMI.[36]
However, evidence is limited and no large randomized controlled trials have been performed or planned. Therefore it remains unclear whether treatment of non-culprit vessel lesions is required and when it should be performed in patients with STEMI.[37] In Chapter 4 published data on these 3 current PCI strategies for multivessel disease in STEMI patients are evaluated.

Part II Impaired microvascular reperfusion

Primary PCI results in around 90% of the cases in complete restoration of epicardial flow. However, despite sufficient epicardial flow, suboptimal microvascular reperfusion is observed in a significant part of the patients after primary PCI.[38] The occurrence of suboptimal microvascular reperfusion has been associated with larger infarct size, lower residual left ventricular ejection fraction, and higher mortality.[38,39] Suboptimal reperfusion is thought to be a multifactorial pathophysiogical process.[8] Potential mechanisms that may

limit optimal microvascular reperfusion are microvascular dysfunction and reperfusion injury. Microvascular dysfunction can be caused by spontaneous and PCI-induced distal embolisation of atherothrombotic material into the distal microvasculature. In addition, microvascular dysfunction can be induced by vasospasm and/or inflammation.[9-11]

Manual thrombus aspiration in STEMI

The high frequency of suboptimal myocardial reperfusion after primary PCI and its association with adverse outcome has resulted in the development of various mechanic and manual devices to protect the microvasculature. Several small randomised controlled trials have been performed, demonstrating that manual thrombus aspiration might be a potential therapy to limit PCI-induced distal embolisation by removing atherothrombotic material exposed to the lumen.[40-42] However, whether thrombus aspiration also results in a significant improvement of myocardial reperfusion and clinical outcome remained unclear.

In chapter 5 the results of the large randomized controlled Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) are presented comparing conventional PCI with thrombus aspiration.[42] In chapter 6 we investigated the one year clinical follow-up of the TAPAS.

The efficacy rates of thrombus aspiration (as defined as successful retrieval of atherothrombotic material) ranges between 73 and 95 percent in published studies.[43,44] Because most of the published studies were not powered to investigate the effect of thrombus aspiration in selected patient subgroups, it is therefore currently unclear what the independent predictors are of effective thrombus aspiration and whether thrombus aspiration should be recommended for use in all patients or in a more selected population. The study presented in chapter 7, investigated what independent predictors are of effective thrombus aspiration in a population treated with routine thrombus aspiration. Uni- and multivariate analyses were performed to identify independent predictors of effective thrombus aspiration, which were subsequently tested for their discriminative and clinical value.

Several manual thrombus aspiration devices are currently available, with different handling characteristics and lumen sizes.[43-45] Currently, it is unknown whether large-lumen-diameter catheters are superior in removing thrombus load when compared with medium-sized ones.

In chapter 8 the results of a prospective cohort study are shown, which investigated whether a large-lumen-diameter catheter is capable of aspirating larger thrombotic components and results in improved angiographic outcome compared to a medium-sized catheter.

Manual thrombus aspiration in non-ST-elevation myocardial infarction (NSTEMI)

Acute coronary syndromes are initiated by an eroded, fissured or ruptured atherosclerotic plaque, leading to subsequent platelet aggregation and thrombus formation. Myocardial necrosis occurs when the resultant thrombus induces epicardial occlusion, but may also be a sign of microvascular obstruction, owing to spontaneous or PCI-induced embolisation.

At the present time, no published data on thrombus aspiration in patients with NSTEMI are available. In chapter 9 the results of a prospective cohort study are presented, in which the feasibility and safety of thrombus aspiration during PCI for NSTEMI were investigated.

Direct stenting

Some studies suggested that stenting without balloon predilatation (direct stenting) might also result in less distal embolisation and improved microvascular reperfusion compared to stenting with predilatation.[46,47] Because in the thrombus aspiration studies the use of thrombus aspiration often resulted in sufficient antegrade coronary flow, predilatation before stenting was often not necessary. This resulted in a higher rate of stenting without predilatation compared to conventional PCI. As direct stenting is suggested to be superior compared to balloon predilatation followed by stenting, the beneficial effect of thrombus aspiration could (partly) be related to the effect of direct stenting. However, it is currently unclear what the value of direct stenting is in the context of primary PCI.
In chapter 10 STEMI patients who underwent direct stenting were compared with patients who underwent thrombus aspiration prior to stenting in routine clinical practice, to investigate whether thrombus aspiration is also beneficial in patients eligible for direct stenting.

Impact of the operator on microvascular reperfusion.

A significant proportion of patients treated with primary PCI for STEMI suffer from serious adverse events such as incomplete myocardial reperfusion.[38,39] Although, patient-related factors play a major role in the occurrence of these adverse events, it is currently unknown to which degree these adverse events are also operator related.[48,49]
Therefore, in chapter 11 inter-operator variation was investigated using objective safety and efficacy endpoints during primary PCI for STEMI. The primary endpoint was incidence of optimal microvascular reperfusion after primary PCI.

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CHAPTER 2

Drug-eluting stents for ST-elevation myocardial infarction

§ 2.1

DES or BMS in acute myocardial infarction?

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INTRODUCTION

The prognosis of patients with acute myocardial infarction (AMI) has been considerably improved following the introduction of reperfusion therapies. The primary aim in the acute phase of an AMI is rapid and sustained restoration of blood flow through the infarct-related artery. When logistically feasible, primary percutaneous coronary intervention (PCI) has emerged as the preferred reperfusion modality. Compared with balloon angioplasty, implantation of a baremetal stent (BMS) results in a lower rate of reocclusion and restenosis. Nevertheless, rates of target vessel revascularization after BMS implantation in patients with AMI range from 7 to 15%.[1,2]

The clinical presentation of the restenotic process is most often recurrence of angina, and is usually not associated with death or myocardial infarction. BMS eliminate elastic recoil and negative remodelling. However, they may induce marked neointima proliferation, resulting in in-stent restenosis. In elective PCI, drug-eluting stents (DES) have been shown to reduce neointima proliferation and thereby the risk of in-stent restenosis. These initial positive outcomes have resulted in widespread use of DES in high-risk patients, such as patients with AMI.

Kastrati et al. have reported their findings on the use of DES for primary PCI.[3] The authors have performed a careful meta-analysis of eight randomized controlled trials (RCTs), comparing DES with BMS in 2786 patients. Individual patient data were available from seven of the eight studies (2476 patients). Therefore, this meta-analysis offers important time to event data regarding revascularization and thrombotic complications. This is of particular importance as it has become clear that DES may be associated with late acute stent thrombosis, a rare event but with often catastrophic clinical consequences. The authors concluded that DES in patients with AMI are effective [hazard ratio (HR) 0.38 for the risk of reintervention, $P < 0.001$] and safe (HR 0.80 for the risk of angiographic stent thrombosis, $P = 0.43$). However, before we can advocate widespread use of DES in patients with AMI, the following issues should be clarified.

Is the external validity of DES vs. BMS trials in acute myocardial infarction compromised?

Do the patients included in the DES vs. BMS trials in AMI represent a general 'all-comers' infarct population? In this regard, there are important differences in trial designs, in particular between PASSION and TYPHOON,[4,5] the two largest trials published to date, contributing together 50% of the patients included in the meta-analysis of Kastrati et al. The PASSION trial reported no exclusion criteria regarding lesion characteristics and investigated DES in a population resembling real-world practice. However, this trial failed to show an advantage in target lesion revascularizaion (TLR) for DES vs. BMS (6.2 vs. 7.4%, $P = 0.23$). In contrast, the TYPHOON trial had a long list of exclusion criteria (previous PCI in the infarct-related vessel, excessive tortuosity or calcification, ostial lesions, birfucation lesions, multiple lesions, massive thrombus in infarct-related vessel, etc.) and found lower rates of target vessel revascularization (TVR) for DES (5.6 vs. 13.4%, $P < 0.001$). These conflicting data strongly suggest that at the present time DES should not be recommended for use in all patients with AMI. As in elective patients, additional

analysis and RCTs of specific patient groups are necessary to assess which patients with AMI benefit from DES implantation and which do not.

Late and very late stent thrombosis (>1 or >3 years after implantation)

The drug and polymer composition of DES causes endothelial dysfunction, delayed endothelial healing, enhanced agonist-induced platelet aggregation, and hypersensitivity reactions.[6–8] Particularly in the context of AMI, these features have raised concerns with regard to the potential higher risk of thrombotic complications when DES are implanted in a prothrombotic environment. Furthermore,the extent of the toxic effect of DES on the healing myocardium in AMI patients is largely uninvestigated.[6,8] Despite these concerns, it should be noted that none of the published RCTs reported an increased risk of angiographic documented or possible stent thrombosis associated with DES.
Noteworthy is that follow-up in most studies was limited to 1 year. A registry of 505 AMI patients from the Rotterdam group showed that the benefit of DES over BMS in terms of TVR was no longer apparent after 3 years follow-up.[9] In this study, late stent thrombosis occurred in four patients (2.1.%) treated with DES in the third year of follow-up against none in the BMS group. This illustrates that, with regard to late stent thrombosis, large populations and longterm follow-up are needed to establish the true incidence of this serious complication.

The clinical outcome of DES after 3–5 years

With the exception of the PASSION trial, all RCTs found an early advantage of DES in AMI, in terms of less angiographic and clinical restenosis. As demonstrated in the previously mentioned Rotterdam registry, late thrombotic events can result in more TVR in DES patients, which can negate the benefit observed in the first years. Because of the suspected higher incidence of very late stent thrombosis associated with DES compared with BMS, there should be reservations regarding conclusions about the effect of DES on long-term clinical outcome, in particular when conclusions are based on trials with follow-up limited to 1 year.

Cost–benefit ratio of DES

Cost-ineffectiveness is a 'complication' of DES implantation which cannot be neglected. The initial costs of the procedure are clearly higher with the use of DES. However, because of the lower need for revascularization procedures, there may be cost savings over the entire course of patient care. Several studies have been published assessing the cost-effectiveness of DES compared with BMS in elective patients. DES were found not to be cost-effective compared with conventional BMS, with the exception of patients at the highest risk of developing restenosis. In addition, in several RCTs, older generation, thick-strut BMS were used as the comparison to evaluate DES in AMI. As demonstrated by Kastrati et al., when two stents with different designs are compared, the stent with the thinner struts is associated with less angiographic and clinical restenosis.[10] The new generation of BMS may therefore be associated with lower restenosis rates, thereby further improving costeffectiveness of BMS compared with DES in AMI.

Long-term follow-up, in terms of death/reinfarction, of the previously described trials together with several important RCTs which are underway, such as HORIZONS AMI [3400 AMI patients randomized to paclitaxel-emitting stents (PES) or BMS] and CEZAR [352 AMI patients randomized to PES or sirolimus-eluting stents (SES)], will be necessary to resolve these issues.

CONCLUSION

The meta-analysis of Kastrati et al.[3] summarizes our current knowledge of RCTs in AMI. It can be concluded that prospective studies with long-term follow-up, RCTs, and large registries will be necessary before we can conclude whether or not DES are associated with improved longterm clinical outcome. Until that time, DES implantation on a routine basis in patients with AMI should not be recommended.

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§ 2.2

Safety and efficacy of drug-eluting stent for ST-segment elevation myocardial infarction in an unselected consecutive cohort

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ABSTRACT

Objective

The objective of this study is to investigate the clinical outcome of a large cohort of patients with ST-segment elevation myocardial infarction (STEMI) treated with drug-eluting stents (DES) compared to bare metal stents (BMS).

Background

Several randomized controlled trials have demonstrated that PCI with the routine use of DES is safe and effective in patients with STEMI. However as randomized trials have strict inclusion criteria, further studies in unselected patient populations are needed.

Methods

We performed a retrospective cohort analysis of the Mayo Clinic PCI database. A total of 552 consecutive STEMI patients who underwent a DES implantation between May 2003 and April 2006 were included in the study and compared to 557 who had BMS for STEMI earlier. No specific patient subsets were excluded.

Results

Procedural success was achieved in 532 patients (96%). During initial hospitalization, 16 patients (2.9%) died and 8 (1.5%) suffered from a recurrent myocardial infarction. The median follow-up was 23 months (IQR: 13–27 months). At 12 months post discharge, the rate of target lesion revascularization and death were 2.9% and 3.7%, respectively, and survival free of major adverse cardiac events (MACE) was 90.9%. These rates were similar to or lower than those of patients treated for STEMI with BMS prior to the availability of DES.

Conclusion

DES are safe and effective in the treatment of STEMI in an unselected cohort; 90.9% of patients are free of MACE at 12months post discharge.

INTRODUCTION

Percutaneous coronary intervention (PCI), with the routine use of drug-eluting stents (DES), has been found to be safe and effective in prospective randomized trials enrolling mainly stable patients, with discrete coronary lesions.[1–3] Since patients with STsegment elevation myocardial infarction (STEMI) have been typically categorically excluded from randomized DES trials, it is currently unclear whether the experience in stable patients can be extrapolated to patients with STEMI.

Small studies assessing the safety and feasibility of DES in STEMI suggest that DES have similar rates of thrombotic complications and lower rates of revascularization when compared to bare metal stents (BMS).[4–10] Recently, two randomized trials have been published with different results: the TYPHOON study identified that sirolimus-eluting stents (SES) significantly reduced rate of target vessel revascularizations (TVR) at one year, while the PASSION trial found only nonsignificant differences.[11,12] Since randomized trials have strict inclusion criteria, further studies in unselected patient populations are needed. Accordingly, we evaluated in hospital and long-term outcome in the Mayo Clinic registry of consecutive patients with STEMI treated with DES.

METHODS

Patients

The study population consisted of patients who underwent DES placement for STEMI at the Mayo clinic, Rochester, Minnesota, in the period from May 2003 to October 2005. A group of patients treated for STEMI with BMS during the time frame January 1999 to March 2003 were also included for comparisonpurposes.

All patients presenting with STEMI and treated with a SES (Cypher, Johnson & Johnson-Cordis) or paclitaxel-eluting stent (PES) (Taxus, Boston Scientific) were included in this study. This included patients presenting in cardiogenic shock and patients undergoing rescue PCI after failed thrombolysis. Patients were only excluded if they refused permission for their records to be used for research, as required by Minnesota state law.

The analysis was approved by the Institutional Review Board.

Procedural Details

PCI was performed using standard percutaneous techniques. Usually, only the infarct related vessel was treated. Predilatation was usually performed prior to stent placement at the operator's discretion. Adjunctive therapy included intravenous heparin during the procedure to achieve an activated clotting time of 200–250 sec with a glycoprotein IIb/IIIa inhibitor and 250–300 sec without a glycoprotein IIb/IIIa inhibitor. A glycoprotein IIb/IIIa inhibitor was administered at operator discretion. Acetylsalicylic acid 325 mg was administered prior to the procedure and continued indefinitely. Clopidogrel was given with a loading dose of 300–600 mg at the beginning of the procedure; it was continued at a dose of 75 mg for at least 6 months after stent implantation.

Table 1. Baseline characteristics and procedural details

Variables	DES (N=552)	BMS (N=577)	P-value
Age (years)	63 ± 14	65 ± 14	0.10
Males	367 (66)	397 (69)	0.41
Pre-procedural shock	66 (12)	94 (16)	0.035
Canadian Heart Class III angina	139 (25)	91 (16)	<0.001
Body mass index (kg/m2)	28.4 ± 5.3	28.9 ± 5.3	0.15
Diabetes mellitus	92 (17)	109 (19)	0.35
Hypertension	324 (66)	325 (60)	0.06
Cholesterol >240 (mg/dl)	319 (69)	345 (72)	0.29
Smoking history			0.37
Former smoker	162 (30)	191 (33)	
Current smoker	191 (36)	182 (32)	
Medical history			
CABG	29 (5)	34 (6)	0.64
MI >7 days	66 (12)	90 (16)	0.08
PTCA	70 (13)	87 (15)	0.24
PVD	34 (6)	32 (6)	0.70
CVA/TIA	42 (8)	46 (8)	0.76
CHF	53 (10)	99 (19)	<0.001
Tumor/lymphoma/leukemia	58 (11)	50 (9)	0.31
Multivessel disease	359 (67)	374 (66)	0.78
Primary PCI	366 (66)	449 (78)	<0.001
Location of the intervention			
Left main coronary artery	3 (0.6)	7 (1.2)	0.23
Left anterior descending coronary artery	228 (41)	256 (44)	0.30
Left circumflex coronary artery	96 (17)	73 (13)	0.026
Right coronary artery	249 (45)	257 (45)	0.85
Vein graft	15 (3)	18 (3)	0.69
No. of stents placed	1.3 ± 0.7	1.5 ± 0.7	0.001
GP IIb/IIIa use	448 (81)	501 (87)	0.007
Thrombectomy	17 (3)	13 (2)	0.39
AngioJet use	18 (3)	27 (5)	0.22

CABG = coronary artery bypass grafting, CHF = congestive hearth failure, CVA = cerebrovascular accident, MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, PVD = peripheral vascular disease, TIA = transient ischemic attack.

MATERIALS

The data were obtained from the Mayo Clinic PCI registry. This computerized registry includes prospectively collected baseline, procedural, and angiographic data on all patients undergoing an interventional procedure in the Cardiac Catheterization Lab at the Mayo Clinic, and has supported multiple outcome studies.
Baseline data collection is accomplished by chart review and includes patient demographics, co-morbidities, in-hospital medications, complications, lesion and device-specific procedural data, and dismissal medications. Follow-up data was collected prospectively post-procedure by telephone interviews at 6 months, 12 months, and yearly thereafter. Follow-up data included symptom status, medications, and cardiac event data. All subsequent cardiac hospitalizations are reviewed by obtaining the medical records from Mayo as well as outside institutions.

Definitions

The primary endpoint of this study was the occurrence of major adverse cardiac events (MACE) at follow-up, defined as all-cause death, target vessel revascularization (TVR) and nonfatal MI. TVR was defined as a repeat intervention (surgical or percutaneous) driven by any lesion located in the same vessel treated at the index procedure. Target lesion revascularization (TLR) was defined as a repeat intervention (surgical or percutaneous) driven by a lesion located in the same segment treated at the index procedure. MI was considered when at least two of the three following criteria were met (1) Prolonged chest pain ≥20 min, (2) enzyme changes (more than double the upper normal limits of Creatine kinase (CK), CK-MB, or Relative Index) (3) ST-T-wave changes or new Q-waves on serial ECGs indicative of myocardial damage. Shock was defined as prolonged systolic blood-pressure <90 while not on inotropes or intra-aortic balloon pump (IABP) support or systolic blood-pressure <110 while on inotropes or IABP support. Procedural success was defined as <20% residual stenosis in the treated lesion with no in-hospital death, Q-wave MI or coronary artery bypass grafting (CABG).

Statistical Methods

Values are shown as means ± standard deviations or numbers of patients (percentages). Follow-up event analyses included only in-hospital survivors, with follow- up starting on the date of discharge. Kaplan-Meier methods were used to estimate event-free survival rates. Comparisons between groups were tested using the two-sample Student's t-test, the Wilcoxon rank sum test, Pearson's χ^2 test, or the log-rank test as appropriate for given data distributions. Logistic regression models were employed to estimate simple and partial odds ratios for the relationship between DES vs. BMS and in-hospital outcomes. Partial odds ratios are adjusted for the Mayo Clinic Risk Score.[13] Similarly, Cox regression models were used to estimate hazard ratios for survival endpoints. For each model, the covariates included were those that had a significant unadjusted association with the endpoint. The candidate variables considered for each Cox model were age, sex, Canadian Heart Class ≥III, history of CHF, diabetes, hypertension, body mass index, history

Table 2. Kaplan-Meier estimates of adverse events at follow-up following successful PCI

Variables	DES (n=536)	BMS (n=557)	P-value
All-cause mortality			0.93
30 days	0.6	0.7	
6 months	1.9	2.7	
12 months	3.7	4.2	
24 months	6.4	6.4	
Any re-MI			0.31
30 days	1.0	1.1	
6 months	2.1	2.6	
12 months	2.7	4.3	
24 months	7.2	5.6	
TVR *			0.002
30 days	1.1	2.4	
6 months	3.1	7.9	
12 months	6.2	10.4	
24 months	7.7	11.5	
TLR			<0.001
30 days	0.8	2.4	
6 months	2.1	7.9	
12 months	2.9	10.4	
24 months	4.7	11.1	
MACE			0.18
30 days	2.3	3.1	
6 months	6.5	10.5	
12 months	9.1	15.3	
24 months	16.3	18.8	

* Including TLR, MACE = major adverse cardiac events, MI = myocardial infarction, TLR = target lesion revascularization, TVR = target vessel revascularization.

of cholesterol >240, history of smoking, history of MI, prior PCI, prior CABG, PVD, history of CVA/TIA, chronic renal disease, COPD, metastatic cancer, LVEF, multivessel disease, thrombus in any lesion, maximum device size used, urgency of PCI, number of segments treated, number of vessels treated, number of stents placed, GPIIb/IIIa use, location of intervention, vein graft intervention, post-PCI TIMI flow of II/III. The proportional hazards assumption was assessed by visual inspection of a smoothed relationship of the scaled Schoenfeld residuals over time. Statistical analyses were completed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Clinical and Angiographic Characteristics

A total of 552 consecutive DES patients and 577 BMS patients were included in the study. Baseline characteristics are detailed in Table I. Patients treated with DES had a mean age of 63 ± 14 years and 66% were men. The BMS patients had similar age/gender distribution. Preprocedural shock was less common in the DES patients (12% vs. 16%, P = 0.035) as was a history of CHF (10% vs. 19%, P < 0.001). Primary PCI was also less common in the DES group (66% vs. 78%, P < 0.001).

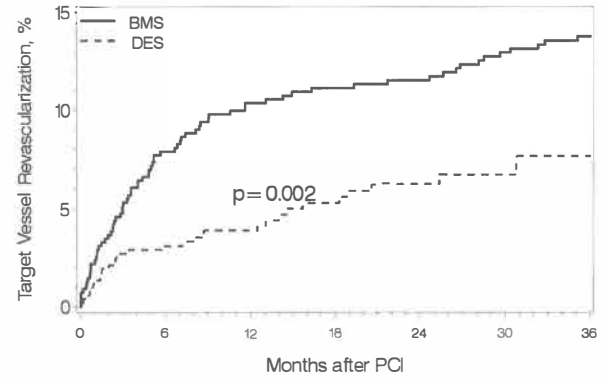
Procedural Details and Outcomes

Fewer stents on average were placed in DES patients than BMS patients (1.3 ± 0.7 vs. 1.5 ± 0.7, P = 0.001). The majority (88%) of DES stents placed were SES stents. A glycoprotein IIb/IIIa receptor inhibitor was used slightly less in the DES patients (81% vs. 87%, P = 0.007). TIMI flow 3 was achieved for all lesions in 97% of the DES procedures, which was significantly better than the BMS procedures (92%, P = 0.001). The procedural success rate was high in both groups, 96% in DES procedures and 95% in BMS, P = 0.31. Sixteen DES patients (2.9%) died inhospital, a proportion similar to the BMS group (n = 20, 3.5%, P = 0.059). The occurrence of MI and inhospital CABG were also similar between the two groups.

Follow-Up

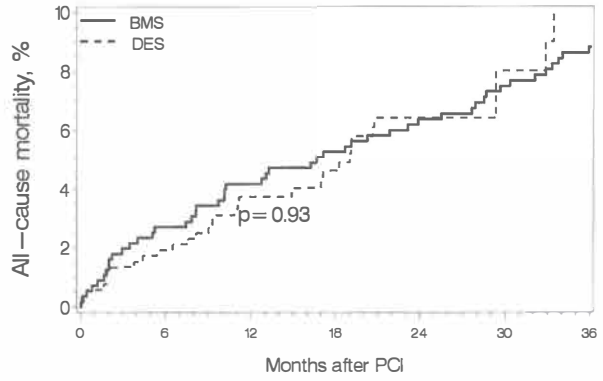
The median period of follow-up after hospital discharge was 23 months (inner quartile range, 13–27 months) for the DES patients. Follow-up is substantially longer in the BMS group (median 61 months, IQR: 49–73) since they represent an earlier patient set. Follow-up at 30 days, 6 months, 1 year, and 2 years was, respectively, 98%, 97%, 84%, and 46% complete in the DES group (all rates were higher in the BMS group). Post-discharge, follow-up outcomes at 30 days, 6 months, and 12 months are listed in Table II. At 12 months, the cumulative incidence of death, any MI, TVR, TLR, and MACE after 12 months was 3.7%, 2.7%, 6.2%, 2.9%, and 9.1% respectively (Table II). Accordingly, the incidence of TVR at 12 months was reduced from 10.4% with BMS to 6.2% with DES, and at 24 months, the corresponding reduction was from 11.5% to 7.7% (Fig. 1). With the endpoint of TLR at 12 months, the incidence was reduced from 10.4% to 2.9% (BMS versus DES) and at 24 months was 11.1% versus 4.7% (P < 0.001). The use of DES was not associated with a significant increase of allcause mortality (P = 0.93) or the combined endpoint of death/reinfarction (P = 0.95) as compared with BMS (Figs. 2 and 3).

Multiple proportional hazards regression models were used to investigate the partial effect of DES use on other follow-up endpoints (Table III). After adjusting for other risk factors, the effects of DES were similar to the unadjusted results, indicating that DES have similar long-term outcomes as BMS with regards to all cause mortality and any MI. The composite endpoint of death, MI, and target vessel revascularization was nearly significantly better (P = 0.055) in the DES treatment group after adjusting for other risk factors.



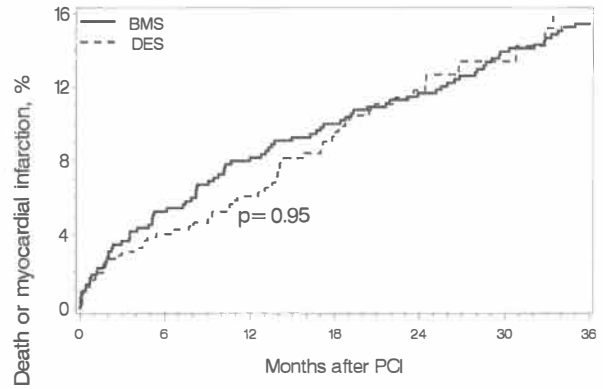
BMS	557	492	470	456	444	428	414
DES	536	493	408	306	209	104	38

Figure 1. Unadjusted Kaplan-Meier Curve for occurrence of target vessel revascularizations



BMS	557	535	525	514	504	494	481
DES	536	509	425	319	221	112	41

Figure 2. Unadjusted Kaplan-Meier Curve for occurrence of all-cause mortality



BMS	557	521	503	488	475	459	446
DES	536	498	414	309	211	106	38

Figure 3. Unadjusted Kaplan-Meier Curve for occurrence of all-cause mortality or any reinfarction

DISCUSSION

This study shows that DES implantation in an unselected population with STEMI results in a low incidence of death, MI, or target lesion or vessel revascularization at 12 months. Unadjusted results of all cause death and MI were similar between BMS and DES. However as is true in other patient subsets at less high risk than STEMI patient, DES continues to be associated with significant decreases in TLR.

There is limited information on the use of DES for STEMI. Until recently, only eight randomized studies on DES implantation in STEMI patients have been published.[4–7,10,11] A recent meta-analysis combined data of four of these studies, but this included only 426 patients treated with SES.[14] This metaanalysis reported an incidence of 7.0% for death, 10.8% for MACE, and 2.3% for TVR after 6–8 months. More recently, Pasceri et al. analyzed seven randomized trials enrolling 2,357 patients with a follow up of 8–12 months.[15] In this analysis, the author identified that the incidence of death or recurrent MI was similar between the two groups, but that TLR was much improved. TLR occurred in 4.8% of DES and 12.0% of BMS (RR 0.40, 95% CI 0.30–0.54). Our population of 536 patients has, despite the performance of rescue PCI after failed thrombolysis in 17.3% and multivessel disease in almost half of the patients, an in hospital mortality rate of 3.7% and a low rate of TLR (2.9%) and MACE (9.1%) at 12 months follow up post-discharge. The 6-month TVR rate (3.1%) in our population is very similar to that reported in the most recent meta analysis.

Table 3. Unadjusted and adjusted hazard ratios and 95% confidence intervals for DES vs. BMS on long-term follow-up

Endpoint	Unadjusted hazard ratio	Adjusted hazard ratio
Death	1.02 (0.65-1.62), p=0.93	0.92[a] (0.57-1.49) p=0.74
Death/re-MI	1.01 (0.72-1.42), p=0.95	0.93[b] (0.65-1.32), p=0.67
MACE	0.82 (0.62-1.09), p=0.18	0.75[c] (0.56-1.01), p=0.055

a. Adjusted for age, gender, angina class, history of CHF, hypertension, BMI, history of MI, prior CABG, PVD, history of CVA/TIA, renal disease, COPD, metastatic cancer, multivessel disease, device size used, no. of segments treated and post-PCI TIMI flow.

b. Adjusted for age, gender, angina class, history of CHF, hypertension, history of MI, prior PCI, prior CABG, PVD, history of CVA/TIA, renal disease, metastatic cancer, multivessel disease, device size, no. of segments treated, PCI in RCA, and PCI in vein graft.

c. Adjusted for age, history of CHF, diabetes, hypertension, BMI, history of MI, prior PCI, prior CABG, history of CVA/TIA, renal disease, metastatic cancer, multivessel disease, device size, no. of segments treated, no of stents placed, post-PCI TIMI flow.

Earlier studies suggest that the drug and polymer composition of DES could cause delayed endothelial healing,[16,17] enhanced agonist-induced platelet aggregation[18] and hypersensitivity reactions.[19] These features raised concerns regarding the risk of stent thrombosis when DES are implanted in an actively thrombotic environment of a STEMI lesion. There were variable results in the two recent randomized trials that could not be detected in our study. In the TYPHOON, the incidence was 3.4%–3.6%, while in PASSION, it was 1% at 1 year.[10,11] Irrespective; in each trial there was no difference between BMS and DES.

Limitations of the study

This retrospective, single-centre study of DES implantation in ST-elevation myocardial infarction, suffers from the limitations inherent to this particular study design. However, given the unselected and large population of DES procedures, it is representative of the daily practice of interventional cardiology. Followup events were not adjudicated to ascertain stent thrombosis rates. The definition used for in-hospital reinfarction may overestimate the actual incidence of reinfarction.

CONCLUSION

The outcome of this study demonstrates excellent outcomes of DES implantation in STEMI with continued significant improvement in TLR and TVR compared with BMS. However, more randomized trials are necessary to confirm the safety and feasibility of DES in the treatment of STEMI.

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CHAPTER 3

Impact of pretreatment with clopidogrel on initial patency and outcome in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review

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ABSTRACT

Background

The main goal of the initial treatment of ST-segment elevation myocardial infarction is prompt reperfusion of the infarct-related artery. The value of pretreatment with clopidogrel before primary percutaneous coronary intervention is currently unclear.

Methods and Results

Studies were retrieved through MEDLINE and Cochrane Controlled Trials Register searches over the past 20 years. Two authors independently performed the study selection and data extraction. Randomized controlled studies were included when the research subjects were unselected patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Pilot trials, studies that enrolled patients undergoing rescue percutaneous coronary intervention, and studies with angiographic assessment not performed by a core laboratory or 2 blinded investigators were excluded. Thirty-eight treatment groups, including 8429 patients, were included. Initial patency was higher in treatment groups in which patients received pretreatment with clopidogrel (34.3%; 95% confidence interval, 32.9 to 35.8) compared with those in which patients did not receive clopidogrel before initial coronary angiography (25.8%; 95% confidence interval, 24.5 to 27.1). In multivariate-weighted logistic regression analysis, pretreatment with clopidogrel was an independent predictor of early reperfusion (odds ratio, 1.51; 95% confidence interval, 1.31 to 1.74; $P<0.0001$) and improved clinical outcome.

Conclusions

Initial patency and clinical outcome were improved in treatment groups that received pretreatment with clopidogrel. These results in patients undergoing primary percutaneous coronary intervention are in line with the experience of pretreatment with clopidogrel in elective patients, non–ST-elevation coronary syndromes, and thrombolytic studies.

INTRODUCTION

The main goal of the initial treatment of ST-segment elevation myocardial infarction (STEMI) is prompt reperfusion of the infarct-related artery. Compared with thrombolysis, primary percutaneous coronary intervention (PCI) in STEMI increases the rate of patency of the infarctrelated artery and reduces the rates of death, reinfarction, and stroke during follow-up.[1] However, PCI remains associated with a significantly longer delay between first medical contact and start of treatment.[2,3] In pursuit of minimizing myocardial damage, antiplatelet and antithrombin agents are often started on site by ambulance or emergency department staff. Early administration of these agents, so-called pretreatment, may result in early reperfusion and more complete platelet inhibition during primary PCI.[4-7] Post hoc analyses of large trials indicate that clinical outcome is improved in patients with patency on the coronary angiogram before primary PCI, suggesting that early reperfusion improves survival.[8]

At the present time, no data have been published on the impact of pretreatment with clopidogrel in the setting of PCI for STEMI. Guidelines and recommendations for pretreatment with clopidogrel are based on experience in acute coronary syndromes and thrombolytic studies.[9] Although data are lacking, pretreatment with clopidogrel is widely used in routine clinical practice. Evidence with regard to impact on early reperfusion and short-term outcome is necessary and should be examined in the context of available data from clinical trials.

We performed a systematic review to compare the incidence of initial coronary artery patency and shortterm outcome in treatment groups of studies in which patients received pretreatment with clopidogrel with those in which patients did not receive clopidogrel before initial coronary angiography.

METHODS

Study Selection and Data Extraction

We performed MEDLINE and Cochrane Controlled Trials Register searches for published articles over the past 20 years using the following keywords and Medical Subject Headings (MeSH) terms: "randomized," "percutaneous coronary intervention," "angioplasty," "stent," "balloon," "dilatat*," "myocard* infarct*," "myocardial infarction" [MeSH], "angioplasty, transluminal, percutaneous coronary" [MeSH], "stents" [MeSH], and "balloon dilatation" [MeSH]. Reference lists of selected articles were reviewed for other potentiallyrelevant citations.

Two independent reviewers (P.J.V. and T.S.) performed the study selection. Studies were selected if they were randomized and controlled; published in English, French, or German; and enrolled unselected patients with STEMI undergoing primary PCI. By unselected, we meant no inclusion or exclusion criteria relative to type of infarction (eg, size and location) or angiographic characteristics (eg, visible thrombus and Thrombolysis in Myocardial Infarction [TIMI] flow). Included studies had to report pre-PCI angiographic and clinical characteristics, symptom duration 24 hours, and information with regard to pretreatment. We excluded pilot trials, studies that enrolled patients undergoing rescue

PCI, and studies in which angiographic data were not assessed by a core laboratory or 2 blinded investigators. Subgroups of included studies reporting optional pretreatment with clopidogrel, pretreatment with glycoprotein IIb/IIIa inhibitor, or fibrinolysis were excluded from the analysis.

Data extraction was performed independently by 2 reviewers (P.J.V. and T.S.) who collected information on study design; baseline clinical characteristics; procedural details; and angiographic, short-term clinical, and safety outcomes. Authors were contacted in case of incomplete or unclear data.

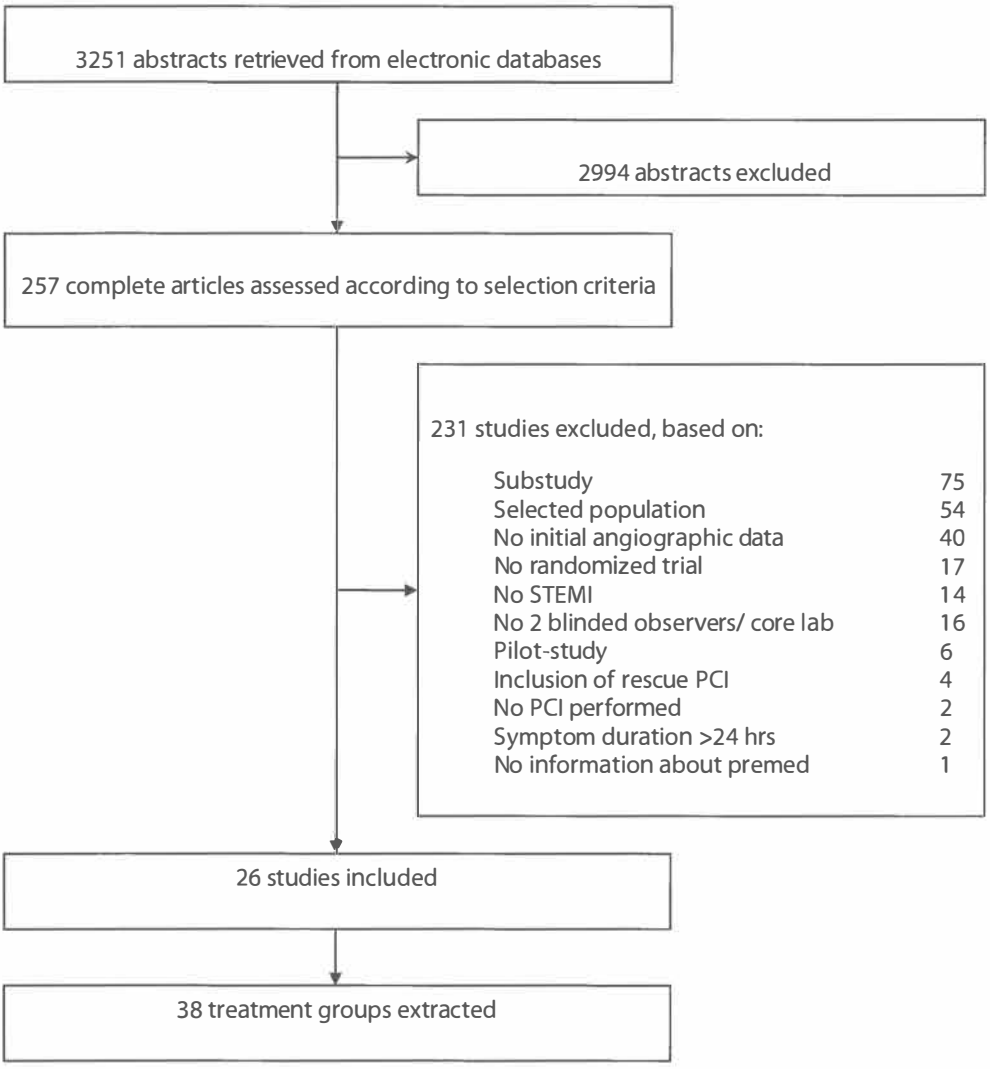

Figure 1. Flow diagram of study inclusion

Table 1. Main characteristics of the included subgroups

Primary author, year of publication	N	Sx duration, hrs	Sx-to-PCI, hrs	Sx-to-admission, hrs	UFH, loading dose	Clopidogrel loading dose, mg	Timing pre-treatment with clopidogrel, hrs	Design	Included subgroup	F-U
Pre-treatment with clopidogrel										
Armstrong, 2006	100	<6	Median 2,9	n/a	Enoxa 1 mg/kg	300	First medical contact-to-Clop: median 0,9 First medical-contact-to-PCI: median 2,1	Lytics vs. rescue PCI vs. pPCI	pPCI	30
Dorr, 2006	13	<12	n/a	Mean 5,0	70 U/kg	300	At emergency department	Excimer laser vs. pPCI	pPCI	No
Dorr, 2006	14	<12	n/a	Mean 6,9	70 U/kg	300	At emergency department	Excimer laser vs. pPCI	Excimer laser	No
Kaltoft, 2006	108	<12	Median 4,0	n/a	10000 U	300	30-60 minutes before arrival at catheterization lab	Thrombectomy vs. pPCI	Thrombectomy	31-40
Kaltoft, 2006	107	<12	Median 3,5	n/a	10000 U	300	30-60 minutes before arrival at catheterization lab	Thrombectomy vs. pPCI	pPCI	31-40
Svilaas, 2008	535	<12	Median 3,2	Median 2,7	5000 U	600	In ambulance or emergency department.	Thrombus aspiration vs. pPCI	Thrombus aspiration	30
Svilaas, 2008	536	<12	Median 3,1	Median 2,6	5000 U	600	In ambulance or emergency department.	Thrombus aspiration vs. pPCI	pPCI	30
Laarman, 2006	310	<6	Mean 3,0	n/a	10000 U	300	Directly at hospital arrival	DES vs. BMS	DES	30
Laarman, 2006	309	<6	Mean 3,0	n/a	10000 U	300	Directly at hospital arrival	DES vs. BMS	BMS	30
Stone, 2002	518	<12	n/a	Median 1,8	5000 U	300 (or 500 Ticlopidine)	Median 2,1	Balloon vs. stent, +/- GPI	Balloon	30
Stone, 2002	528	<12	n/a	Median 1,6	5000 U	300 (or 500 Ticlopidine)	Median 2,0	Balloon vs. stent, +/- GPI	Balloon + GPI	30
Stone, 2002	512	<12	n/a	Median 1,9	5000 U	300 (or 500 Ticlopidine)	Median 2,0	Balloon vs. stent, +/- GPI	Stent	30
Stone, 2002	524	<12	n/a	Median 1,8	5000 U	300 (or 500 Ticlopidine)	Median 2,0	Balloon vs. stent, +/- GPI	Stent + GPI	30
No pre-treatment with clopidogrel										
Bucciarelli, 2006	73	<24	Mean 5,6	n/a	n/a	No		GIP vs. placebo	All	No
Gibson, 2006	142	<6	n/a	n/a	60 U/kg	No		Early vs. late GPI	Late GPI	30
Gabriel, 2006	38	<12	Mean 4,1	n/a	5000 U	No		Early vs. late GPI	Late GPI	30
Silva, 2006	74	<12	Mean 3,4	n/a	60 U/kg	No		Thrombus aspiration vs. pPCI	Thrombus aspiration	Inh
Silva, 2006	74	<12	Mean 3,3	n/a	60 U/kg	No		Thrombus aspiration vs. pPCI	pPCI	Inh

(Continued)

Table 1. Continued

Primary author, year of publication	N	Sx duration, hrs	Sx-to-PCI, hrs	Sx-to-admission, hrs	UFH, loading dose	Clopidogrel loading dose, mg	Timing pre-treatment with clopidogrel, hrs	Design	Included subgroup	F-U
Tolg, 2006	50	<8	Mean 4,7	n/a	5000 U	No		Metoprolol vs. Carvediol	Metoprolol	14
Tolg, 2006	49	<8	Mean 5,6	n/a	5000 U	No		Metoprolol vs. Carvediol	Carvediol	14
Inoue, 2005	75	<12	n/a	Mean 3,7	5000 U	No		Lytics-pre vs. pPCI	pPCI	30
Ishii, 2005	185	<24	Mean 4,8	n/a	3000 U	No		Nicorandil vs. placebo	Nicorandil	No
Ishii, 2005	183	<24	Mean 4,5	n/a	3000 U	No		Nicorandil vs. placebo	Placebo	No
Parodi, 2005	66	<12	Mean 3,5	n/a	70 U/kg	No		Clopidogrel vs. ticlopidine	Clopidogrel	30
Parodi, 2005	67	<12	Mean 3,1	n/a	70 U/kg	No		Clopidogrel vs. ticlopidine	Ticlopidine	30
Gyongyosi, 2004	27	<6	n/a	Mean 1,7	60 U/kg	No		Early vs. late GPI	Late GPI	30
van't Hof, 2004	256	<6	Median 3,3	n/a	5000 U	No		Early vs. late GPI	Late GPI	30
Andersen, 2003	790	<12	*Median 3,4	n/a	10000 U	No		Lytics vs. pPCI	pPCI	30
Cutlip, 2003	30	<12	n/a	Median 2,1	n/a	No		Early vs. late GPI	Late GPI	30
Widimsky, 2003	429	<12	Mean 4,7	n/a	200 U/kg	No		Lytics vs. pPCI	pPCI	30
Bonnefoy, 2002	421	<6	Median 3,2	n/a	5000 U	No		Lytics vs. pPCI	pPCI	30
Montalescot, 2001	151	<12	n/a	n/a	70 U/kg	No		GPI-pre vs. placebo	All	30
Liem, 2000	299	<6	Median 3,3	Median 2,0	300 U/kg	No		High vs. low dose heparin	High dose heparin	Inh
Liem, 2000	285	<6	Median 3,5	Median 2,0	5000 U	No		High vs. low dose heparin	Low dose heparin	Inh
Schomig, 2000	71	<12	n/a	Median 2,5	5000 U	No		Lytics vs. pPCI	pPCI	30
Widimsky, 2000	101	<6	Mean 3,6	Mean 2,0	10000 U	No		Lytics vs. rescue PCI vs. pPCI	pPCI	30
Ross, 1999	304	<6	n/a	Median 1,4	5000 U	No		Lytics-pre vs. pPCI	pPCI	30
Vermeer, 1999	75	<6	Mean 3,6	n/a	10000 U	No		Lytics vs. rescue PCI vs. pPCI	pPCI	42

Sx indicates symptom onset; UFH, unfractionated heparin; Clop, clopidogrel; lab, laboratory; pPCI, primary PCI; NA, not available; DES, drug-eluting stents; BMS,bare metal stents; GPI, glycoprotein IIb/IIIa inhibitor; Inh, in hospital; and Pre, premedication.

*Estimated value between 2 medians.

End Points and Definitions

The primary end point was initial coronary artery patency before primary PCI. Secondary end points were short-term mortality, death/reinfarction, and in-hospital major bleeding. Pretreatment with clopidogrel was defined as any thienopyridine given before the initial coronary angiogram. Coronary artery patency was defined as TIMI grade 2/3 flow on the initial coronary angiogram. Major bleeding was defined as the need for blood transfusion during hospitalization. Unless otherwise specified, mortality included both cardiac and noncardiac deaths. Reinfarction rates were defined as reported in the trials.

Statistical Analysis

Percentages and absolute numbers of primary and secondary end points were calculated for each treatment group separately and all groups combined. Corresponding exact 95% confidence intervals (CIs) for single proportions were determined according to the Wilson method.10 In univariate analysis, the treatment effect of clopidogrel was calculated by using weighted logistic regression analysis. For this analysis, treatment groups were split into 2: the group that did and the group that did not experience the end point as defined by the number of patients presented in the individual studies. Logistic regression was then performed, with the outcome variable being end point reached (yes versus no) weighted on number of patients in the subgroups. To account for baseline differences between the (nonrandomized) treatment groups of selected studies and to investigate the robustness of our findings, we carried out a number of secondary analyses. First, we constructed a multivariate-weighted logistic regression analysis, including baseline demographic variables available.

Second, jackknife estimation was used to establish the robust-ness of the reatment effect in the multivariate model. Finally, we calculated a propensity score based on matching of all baseline demographic variables. Missing demographic values were imputed with expectation maximization as the estimation method. All probability values were 2 tailed, with statistical significance set at 0.05. Analyses were performed with SPSS version 12.0.2 (SPSS Inc, Chicago, Ill) and STATA version 10 (STATA Corp, College Station, Tex).

P.J. Vlaar and K. Damman had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

RESULTS

Twenty-six randomized controlled studies met our inclusion criteria (Figure 1).[11-36] Thirty-eight treatment groups comprising 8429 patients were extracted. All 8429 patients were pretreated with heparin and aspirin. Before pre-PCI coronary angiography, 4114 of the 8429 patients received a loading dose of clopidogrel. In 1 study, patients were pretreated with 600 mg clopidogrel[36] (see Table 1). In all other included studies, a 300-mg loading dose of clopidogrel was given as pretreatment (In 1 study,[26] ticlopidine 500 mg also was allowed). In the 4315 patients not pretreated, clopidogrel was administrated after PCI to all patients who underwent stent placement. All included studies were randomized controlled trials; however, differences were found with regard to trial design.

Table 2. Patency on the initial coronary angiogram prior to PCI and clinical outcome at 30 days

		TIMI grade 2/3		Mortality		Death/reinfarction		Major bleeding	
Primary author	Subgroup	%	n/total	%	n/total	%	n/total	%	n/total
		Pre-treatment with clopidogrel							
Armstrong	pPCI	29.6%	29/98	1.0%	1/100	4.0%	4/100		n/a
Dorr	pPCI	53.8%	7/13		n/a		n/a		n/a
Dorr	Excimer laser	21.4%	3/14		n/a		n/a		n/a
Kaltoft	Thrombus aspiration	31.7%	33/104	0.0%	0/108	0.0%	0/108	1.9%	2/108
Kaltoft	pPCI	31.4%	33/105	0.9%	1/107	1.9%	2/107	0.0%	0/107
Svilaas	Thrombus aspiration	45.2%	238/526	2.1%	11/529	2.8%	15/529	3.8%	20/529
Svilaas	pPCI	40.5%	215/531	4.0%	21/531	5.1%	27/531	3.4%	18/531
Laarman	DES	29.4%	91/310	2.6%	8/308	3.2%	10/308		n/a
Laarman	BMS	28.5%	88/309	4.2%	13/306	4.9%	15/306		n/a
Stone	Balloon	29.0%	150/518	2.5%	13/518	3.3%	17/518	3.7%	19/518
Stone	Balloon+GPI	33.3%	176/528	1.1%	6/528	1.9%	10/528	5.1%	27/528
Stone	Stent	32.0%	164/512	2.1%	11/512	3.1%	16/512	4.1%	21/512
Stone	Stent+GPI	34.0%	178/524	2.7%	14/524	3.4%	18/524	5.0%	26/524
Total		34.3%	1405/4092	2.4%	99/4071	3.3%	134/4071	4.2%	131/3142
		No pre-treatment with clopidogrel							
Bucciarelli	All	6.8%	5/73		n/a		n/a		n/a
Gibson	Late GPI	36.6%	52/142	2.8%	4/142	4.2%	6/142	7.0%	10/142
Gabriel	Late GPI	26.3%	10/38	13.2%	5/38	15.8%	6/38	7.9%	3/38
Silva	Thrombus aspiration	18.9%	14/74	0.0%	0/74	0.0%	0/74		n/a
Silva	pPCI	27.0%	20/74	0.0%	0/74	0.0%	0/74		n/a
Tolg	Metoprolol	18.0%	9/50	0.0%	0/50*	2.0%	1/50		n/a
Tolg	Carvediol	20.4%	10/49	2.0%	1/49*	2.0%	1/49*		n/a
Inoue	pPCI	29.3%	22/75	5.3%	4/75*	8.0%	6/75		n/a
Ishii	Nicorandil	15.7%	29/185		n/a		n/a		n/a
Ishii	Placebo	15.3%	28/183		n/a		n/a		n/a
Parodi	Clopidogrel	19.7%	13/66	1.5%	1/66	3.0%	2/66		n/a
Parodi	Ticlopidine	22.4%	15/67	3.0%	2/67	3.0%	2/67		n/a
Gyongyosi	Late GPI	33.3%	9/27	0.0%	0/27	3.7%	1/27		n/a
van't Hof	Late GPI	33.6%	82/244	0.8%	2/247	1.6%	4/247		n/a
Andersen	pPCI	32.0%	253/790	6.6%	52/790	8.2%	65/790		n/a
Cutlip	Late GPI	26.7%	8/30	3.3%	1/30	6.7%	2/30	6.7%	2/30
Widimsky (Prague-2)	pPCI	31.0%	133/429	6.8%	29/429	8.2%	35/429		n/a
Bonnefoy	pPCI	19.6%	77/393	4.8%	20/421	6.4%	27/421		n/a
Montalescot	All	10.9%	10/92	6.6%	10/151	7.9%	12/151		n/a
Liem	High dose heparin	21.7%	65/299	2.7%	8/299	4.0%	12/299	10.0%	30/299
Liem	Low dose heparin	21.1%	60/285	4.2%	12/285	9.1%	26/285	6.0%	17/285
Schomig	pPCI	19.7%	14/71	4.2%	3/71	7.0%	5/71		n/a
Widimsky (Prague-1)	pPCI	26.7%	27/101	6.9%	7/101	7.9%	8/101		n/a
Ross	pPCI	33.9%	103/304	3.3%	10/304	5.9%	18/304		n/a
Vermeer	pPCI	23.6%	17/72	6.7%	5/75	8.0%	6/75		n/a
Total		25.8%	1085/4213	4.6%	176/3865	6.3%	245/3865	7.8%	62/794

Abbreviations as in Table 1. *Only cardiac deaths were reported.

Angiographic End Point

The incidence of patients with TIMI grade 2/3 flow on initial angiography was higher in patients receiving pretreatment with clopidogrel (34.3%; 95% CI, 32.9 to 35.8) compared with control patients (25.8%; 95% CI, 24.5 to 27.1; Table 2 and Figure 2). The unadjusted treatment effect of clopidogrel on early patency was an odds ratio (OR) of 1.53 (95% CI, 1.39 to 1.68; P0.0001; Table 3). In multivariate analysis, clopidogrel pretreatment remained significantly associated with a higher percentage of patients with TIMI grade 2/3 flow (OR, 1.51; 95% CI, 1.31 to 1.74; P<0.0001). Jackknife estimation of the multivariate model and the propensity score–adjusted logistic regression analysis showed similar results (Table 4).

Clinical and Safety Outcomes

Short-term follow-up ranged from in-hospital to 42 days after PCI (Table 1). Mortality was lower in patients receiving pretreatment with clopidogrel (2.4%; 95% CI, 2.0 to 3.0) compared with control patients (4.6%; 95% CI, 3.9 to 5.3). The combined end point of death/reinfarction also was lower in patients pretreated with clopidogrel (3.3%; 95% CI, 2.8 to 3.9) compared with control patients (6.3%; 95% CI, 5.6 to 7.2). The unadjusted treatment effect of clopidogrel was an OR of 0.52 (95% CI, 0.41 to 0.67; P<0.0001) for mortality and an OR of 0.50 (95% CI, 0.40 to 0.62; P<0.0001) for death/reinfarction (Table 3). In all multivariate logistic models, pretreatment with clopidogrel remained significantly associated with lower rates of mortality and death/reinfarction incidence (Table 4). A proper analysis of the end point of major bleeding was not possible because only a minority of the studies supplied data on this end point.

Table 3. The effect of pre-treatment with clopidogrel on early reperfusion and adverse event rates in univariate weighted logistic regression analysis

	Unadjusted treatment effect		
	OR	(95%CI)	p-value
TIMI-2/3	1.53	1.39 – 1.68	<0.0001
Mortality	0.52	0.41 – 0.67	<0.0001
Death/Reinfarction	0.50	0.40 – 0.62	<0.0001

OR = Odds ratio for occurrence of either TIMI-2/3, Mortality and Death/Reinfarction for pre-treatment with clopidogrel.

DISCUSSION

This systematic review found a higher initial patency rate and improved clinical outcome in terms of mortality and death/reinfarction in treatment groups that received pretreatment with clopidogrel.

Currently, the optimal timing to start therapy with clopidogrel for primary PCI in patients with STEMI is unclear. Substantial platelet inhibition can be achieved within 2 hours after a 300-mg loading dose of clopidogrel.[37–39] Because primary PCI remains limited by a time delay of 1 to 2 hours between the first medical contact and PCI, the time is theoretically sufficient to achieve effective platelet inhibition during PCI with a 300-mg loading dose of

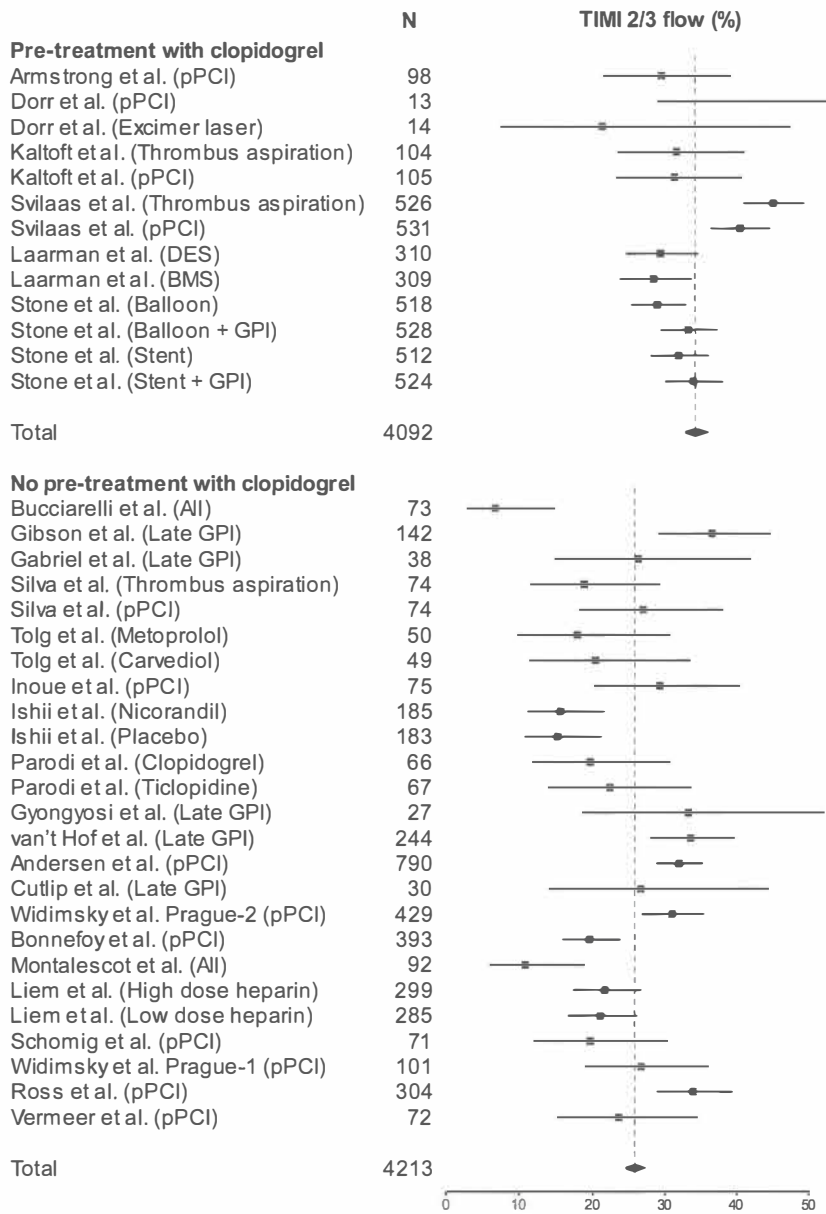

Figure 2. Forrest-tree plot of primary end point. Percentages of TIMI grade 2/3 flow with corresponding 95% CIs for single proportions are shown for each treatment group separately and for all groups combined. pPCI indicates primary PCI; DES, drugeluting stent; BMS, bare metal stent; and GPI, glycoprotein IIb/IIIa inhibitor.

clopidogrel. Therefore, this may have an impact on initial patency rate.[4,39,40] Furthermore, platelet inhibition in patients undergoing primary PCI is important because it will translate to better procedural outcome, eg, by prevention of periprocedural infarct extension.[6,7,38,39] However, because patients with STEMI may have enhanced platelet reactivity, they may require more aggressive platelet inhibition. In addition, several studies have demonstrated a faster onset of platelet inhibition and increased clinical effect of a 600-mg compared with a 300-mg loading dose.[5,39,41]

Table 4. Effect of pre-treatment with clopidogrel on early reperfusion and adverse event rates in multivariate and propensity score adjusted weighted logistic regression analysis

	Multivariate adjusted treatment effect*			Jacknife estimation*			Propensity score adjusted treatment effect		
	OR	(95%CI)	p-value	OR	(95%CI)	p-value	OR	(95%CI)	p-value
TIMI-2/3	1.51	1.31 – 1.74	<0.0001	1.51	1.31 – 1.74	<0.0001	1.53	1.39 – 1.68	<0.0001
Mortality	0.57	0.38 – 0.85	0.0055	0.57	0.40 – 0.81	0.0019	0.52	0.41 – 0.67	<0.0001
Death/Reinfarction	0.54	0.38 – 0.75	0.0003	0.54	0.39 – 0.73	0.0001	0.50	0.40 – 0.62	<0.0001

*Adjusted for Age, Gender, history of Diabetes, history of Hypertension, Heparin dose (high vs. low dose), Symptom duration, Smoking and Year of publication. OR = Odds ratio for occurrence of either TIMI-2/3, Mortality and Death/Reinfarction for pre-treatment with clopidogrel.

The clinical effect of pretreatment with clopidogrel has been investigated only in the context of elective patients, acute coronary syndromes, and thrombolytic studies. In elective patients, pretreatment with clopidogrel before stenting reduced the incidence of acute thrombotic complications and improved clinical outcome.[42-44] In the context of acute coronary syndromes, the Percutaneous Intervention in the Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study demonstrated that pretreatment with a 300-mg loading dose of clopidogrel (given for a median of 6 days before PCI) significantly reduced the incidence of major adverse cardiovascular events.[45] In addition, a substudy of this trial indicated that the benefit of pretreatment with clopidogrel was independent of the timing of PCI. The lowest absolute event rate was seen in patients treated within 48 hours before PCI.[46] In patients treated with thrombolysis for STEMI, additional administration of a 300mg loading dose of clopidogrel resulted in a higher patency rate of the infarct-related artery and reduced the incidence of ischemic complications.[40]

At the present time, no randomized controlled data are available with regard to the impact of pretreatment with clopidogrel before PCI in patients with STEMI. Our systematic review found a higher initial patency rate and improved clinical outcome in treatment groups that received pretreatment with clopidogrel. With an overall sample size of 8429 patients, our review has adequate power for initial patency, mortality, and death/reinfarction. In addition, the clinical benefits of pretreatment with clopidogrel outweigh the increased risk of perioperative blood loss in the subset of patients who are referred to cardiac surgery.[47]

Study Limitations

This systematic review compared treatment groups of studies in which patients received pretreatment with clopidogrel with those in which patients did not and therefore is not a substitute for pooled analyses of individual patient data or a meta-analysis of randomized controlled trials. In addition, the inclusion of studies with different trial designs, PCI strategies (balloon angioplasty, stenting, excimer laser, thrombus aspiration), and pharmacological therapies during and after PCI (glycoprotein IIb/IIIa inhibitors, -blockers, angiotensin-converting enzyme inhibitors) could have induced heterogeneity in our results. The results and conclusions of this analysis should be interpreted with these limitations in mind. However, we have carried out extensive analyses to assess the robustness of our findings. In these analyses, clopidogrel pretreatment was consistently associated with higher rates of TIMI grade 2/3 flow, lower mortality, and lower death/reinfarction rates. Another limitation was that multivariate analysis was possible for only a limited number of variables. Thus, the influence of some relevant variables such as symptom-to-balloon and symptom-to-drug times could not be analyzed. In addition, data on major bleeding were available in only a limited number of subgroups.

CONCLUSIONS

Initial patency and clinical outcome were improved in treatment groups that received pretreatment with clopidogrel. These results in patients undergoing primary PCI are in line with the experience of pretreatment with clopidogrel in elective patients, non–ST-elevation coronary syndromes, and thrombolytic studies.

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CHAPTER 4

Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-elevation myocardial infarction. A pairwise and network meta-analysis

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ABSTRACT

Objectives

To investigate if in patients with ST-elevation myocardial infarction (STEMI) and multivessel disease (MVD), (1) PCI should be confined to the culprit or also non-culprit vessels, and (2) when performing PCI for non-culprit vessels, should this take place during primary PCI or staged procedures.

Background

A significant percentage of STEMI patients have MVD. However, the best PCI strategy for non-culprit vessel lesions is unknown.

Methods

Pairwise and network meta-analyses were performed of 3 PCI strategies for MVD in STEMI patients: (1) culprit vessel only PCI strategy (Culprit-PCI): defined as PCI confined to culprit vessel lesions only, (2) Multivessel PCI strategy (MV-PCI): PCI of culprit vessel as well as ≥1 non-culprit vessel lesion and (3) Staged PCI strategy (Staged-PCI): PCI confined to culprit vessel, after which ≥1 non-culprit vessel lesions are treated during staged procedures. Prospective and retrospective studies were included when research subjects were patients with STEMI and MVD, undergoing PCI. The primary endpoint was short-term mortality.

Results

Four prospective and 14 retrospective studies, involving 40,280 patients, were included. Pairwise meta-analyses demonstrated that Staged-PCI was associated with lower short- and long-term mortality as compared with Culprit-PCI and MV-PCI. MV-PCI was associated with highest mortality rates at both short- and long-term follow-up. In network analyses, Staged-PCI was also consistently associated with lower mortality.

Conclusions

This meta-analysis supports current guidelines discouraging performance of multivessel primary PCI for STEMI. When significant non-culprit vessel lesions are suitable for PCI, they should only be treated during staged procedures.

INTRODUCTION

The primary objective of percutaneous coronary intervention (PCI) in patients with ST-elevation myocardial infarction (STEMI) is to restore epicardial flow and myocardial perfusion in the culprit vessel. However, the pathophysiological process of myocardial infarction is not limited to the culprit vessel.[1] It is estimated that 40-65% of the patients presenting with STEMI have multivessel disease (MVD), which has been associated with worse clinical outcome as compared with single vessel disease.[2] Patients with MVD have in addition to the culprit lesion, one or more significant lesions in non-culprit vessels. When non-culprit vessel lesions are suitable for PCI and coronary artery bypass grafting (CABG) is not preferred, they can be treated according to 3 different strategies. After having treated the culprit vessel, the operator can choose to treat non-culprit vessel lesions conservatively, directly by means of a multivessel PCI or during staged PCI procedures.
Although current international guidelines do not recommend performance of PCI for non-culprit vessels in patients unless there is hemodynamic instability (class III, level of evidence C),[3,4] no large randomized controlled trials have been performed or planned comparing these 3 strategies. Therefore, it remains uncertain whether treatment of non-culprit vessels is required and when it should be performed in patients presenting with STEMI.

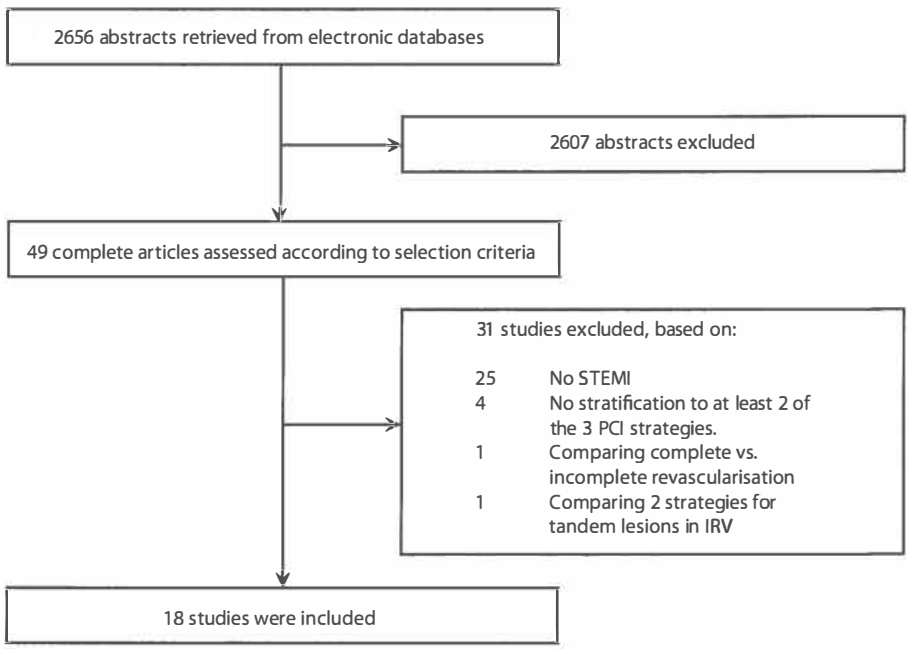

Figure 1. Flow diagram of study inclusion

Recently several small prospective and large retrospective studies have been published comparing these strategies. To evaluate the composite data we performed a systematic

review of all published data to summarize current evidence for these 3 current PCI strategies for MVD in STEMI patients. Pairwise meta-analyses were performed to compare these PCI strategies and an additional network analysis was carried out to investigate the robustness of the pairwise meta-analyses, to combine both direct and indirect evidence, and to rank these 3 PCI strategies.

METHODS

Definitions of the 3 PCI strategies

The 3 PCI strategies for STEMI patients with MVD were defined as follows:

1. The culprit vessel only PCI (Culprit-PCI) strategy was defined as PCI confined to culprit vessel lesions only.
2. The Multivessel PCI (MV-PCI) strategy was defined as PCI in which lesions in the culprit vessel as well as ≥1 non-culprit vessel lesion were treated. All interventions should have had taken place within the same procedure.
3. The Staged PCI (Staged-PCI) strategy was defined as PCI confined to culprit vessel lesions only, after which ≥1 lesions in non-culprit vessel were treated during planned secondary procedure(s). The timing of staged PCI procedures was defined as reported in each study (see table 1).

In studies investigating solely Culprit-PCI versus MV-PCI the primary focus was often only on the strategy during the initial procedure and no details were given about whether or not planned staged procedures were allowed in patients treated according to the Culprit-PCI strategy. In these cases, studies were included but the applied definitions were extracted and used as quality indicator. Authors were contacted in case of unclear definitions.

Study selection

MEDLINE and Cochrane Controlled Trials Register searches were performed to identify relevant articles published between 1985 and August 2010. The following keywords and Medical Subject Headings (MeSH)-terms were used: *"Percutaneous coronary intervention", "Angioplasty", "Stent", "Balloon", "Dilatat*", "Multivessel", "Multi-vessel", "staged", "culprit", "infarct-related", "Myocard* infarct*", "Myocardial Infarction[MeSH]", "Angioplasty, Transluminal, Percutaneous Coronary[MeSH]", "Stents[MeSH]",* and *"Balloon Dilatation[MeSH]".* Reference lists of selected articles were reviewed for other potentially relevant articles. Two independent reviewers (P.V. and K.M.) performed the study selection. Both prospective and retrospective studies were considered for inclusion. Studies were selected if the study (sub)group consisted of STEMI patients with MVD who underwent acute PCI. At least survival data had to be available and stratified to at least 2 of the 3 PCI strategies for MVD. Studies investigating the impact of completeness of revascularisation (so comparing complete versus incomplete revascularisation) or surgical revascularisation for MVD were excluded. In addition, studies investigating PCI in elective patients and acute coronary syndromes with MVD were also excluded. No studies were excluded based on baseline or angiographic criteria.

Table 1. Main characteristics of included studies

Prim author, publication	Setting	Sx-time, hr	PCI Strategies, n: Culprit-PCI	MV-PCI	Staged-PCI	Timing of staged PCI	Exclusion criteria	FU,max
Prospective studies								
Di Mario,2004	Multicenter	12	17	52	-	-	LM, shock, CTO, lesions located in graft or previously treated with PCI, thrombolytic therapy before PCI. No culprit lesion suitable for stenting. Diffuse calcification, severe tortuosity, risk of side branch occlusion.	1 yr
Ochala,2004	Single center	12	-	48	44	27.3±12.8 days	LM, shock, previous CABG, severe valvular disease, no PCI possible in non-culprit vessel (diffuse >4 cm, diameter<2.5mm, severe tortuosity, lesion within orifices of large side branch) renal insufficiency or 1 kidney, contraindications for antiplatelet therapy, pregnancy.	6 m
Politi,2010	Single center	24	84	65	65	56.8±12.9 days	LM, shock, previous CABG, severe valvular disease, unsuccessful culprit PCI	2.5±1.4 yr
Khattab,2008	Single center	12	45	28	-	-	LM, CTO, previous MI, non-culprit vessel diameter<2.5mm, extensive calcification	1 yr
Retrospective studies								
Cavender,2009	Multicenter	All	25802	3134	-	-	LM, thrombolytic therapy before PCI, staged PCI.	Inhosp.
Corpus,2004	Single center	12	354	26	126	Inhospital	LM, PCI in vein graft or for acute occlusion after coronary angioplasty, staged PCI after hospital discharge.	1 yr
Dziewier,2010	Multicenter	-	707	70	-	-	Previous CABG.	1 yr
Han,2008	Single center	-	149	-	93	7-15 days	LM, shock, pulmonary edema, cardiac rupture.	1 yr
Hannan,2010*	Multicenter	24	3262	503	259	Inhospital	LM, shock, previous open heart surgery, thrombolytic therapy before PCI, missing ejection fraction.	3,5 yr
Kong,2006	Multicenter	24	1350	632	-	-	LM, shock or hemodynamic instability, cardiopulmonary resuscitation, previous MI/PCI/CABG.	Inhosp.
Mohamad,2010	Single center	12	30	7	12	n/a	Unable to undergo CAG<3 hrs of hospital presentation.	1 yr
Poyen,2003	Single center	12	81	86	-	-	Shock.	2,5 yr
Qarawani,2008	Single center	12	25	95	-	-	LM, shock.	1 yr
Rigattieri,2007	Single center	12	46	-	64	Inhospital	LM, shock, previous CABG, severe valvular disease.	1 yr

(Continued)

Table 1. Continued

Prim author, publication	Setting	Sx-time, hr	PCI Strategies, n Culprit-PCI	MV-PCI	Staged-PCI	Timing of staged PCI	Exclusion criteria	FU,max
Roe,2001	Multicenter		79	79	-	-	LM, PCI of side branch.	
Schaaf,2010	Single center	6	124	37	-	-	Patients without shock.	1 yr
Toma,2010	Multicenter	6	1984	217	-	-	LM, second PCI in culprit vessel, rescue PCI, isolated inferior MI, serious comorbidity, pregnancy or breastfeeding.	3 m
Varani,2008	Single center	24	156	147	96	Inhospital	PCI for acute occlusion after coronary angioplasty.	1.7±1.0 yr

*Different matched populations are used in the pairwise comparisons. CTO=chronic total occlusion, FU=duration of available follow-up, LM=left main stenosis, MI=myocardial infarction, n/a=data not available, shock=cardiogenic shock defined as reported in the studies, Sx-time=time between symptom onset and hospital admission.

Data extraction

Data extraction was performed independently by 2 researchers (P.V. and K.M.). Information was collected with regard to study design, quality indicators, baseline clinical characteristics, procedural details, clinical outcomes and safety outcomes. Authors were contacted in case of incomplete or unclear data.

Endpoints

The primary endpoint was short-term (inhospital/30 days) mortality. Secondary endpoints were long-term mortality, reinfarction, any revascularization, major bleeding and stroke. Unless otherwise specified, mortality included both cardiac and non-cardiac death. Stroke included both ischemic and hemorrhagic stroke. Major bleeding was defined as the need for blood-transfusion during hospitalization. Reinfarction as well as MVD and cardiogenic shock were defined as reported in the studies.

Statistical methods

Absolute numbers and percentages of the endpoints were calculated for each study separately and all studies combined. For the direct pairwise meta-analyses, pooled estimates and 95% confidence intervals (CI) were calculated assuming a random-effects model with inverse-variance weighting using the DerSimonian and Laird method to account for heterogeneity. The following pairs were analyzed: Culprit-PCI vs. MV-PCI, Culprit-PCI vs. Staged-PCI and MV-PCI vs. Staged-PCI. Heterogeneity across studies was tested by the Cochran's Q statistic and the I2 statistic. Funnel plots were used to assess potential publication bias. Subgroups were made based on design (prospective and retrospective studies) and shown for each comparison and endpoint. A subanalysis was performed on Culprit-PCI vs. MV-PCI in cardiogenic shock patients. Pairwise analyses were performed using Review Manager (version 5.0.24).

A network analysis[5-7] was carried out to investigate the robustness of our findings and to combine both direct and indirect evidence about the 3 PCI strategies. The analysis was carried out using three types of random effects models: a consistency model,[7] an inconsistency model,[7] and a node-splitting model.[8] Vague priors were specified in all of the models: $N(0, 1000)$ for effect parameters and $U(0, 4)$ for variance parameters. As the evidence structure is a triangle, there is only one inconsistency factor w in the inconsistency model. In the node-splitting model, we split the node $d_{m,s}$ (MV-PCI vs. Staged-PCI) into direct evidence $d\frac{Dir}{m,s}$ and $d\frac{Ind}{m,s}$ indirect evidence. Inconsistency was assessed by (1) comparing deviance information criterion model fit accross the 3 models,[7] (2) testing $w \neq 0$,[7] and (3) testing $d\frac{Dir}{m,s} \neq d\frac{Ind}{m,s}$.[8] Both hypothesis tests were performed using the `Bayesian P value'.[8] All models were computed using Markov Chain Monte Carlo simulation in JAGS[9] and R[10] using three chains with over dispersed initial values. The models were run for 300,000 iterations, after which convergence was assessed using the Brooks-Gelman-Rubin diagnostic.[11] After this, all inference was based on a further 100,000 iterations.
All p values were 2-tailed, with statistical significance set at <0.05. This meta-analysis was performed in compliance with published recommendations for meta-analyses.[12]
P.J. Vlaar and G. van Valkenhoef had full access to and take full responsibility for the integrity of the data.

RESULTS

Eighteen studies, involving 40,280 patients, met our inclusion criteria (figure 1).[13-30] All included STEMI patients with MVD underwent PCI. Of the 18 included studies, 4 studies were prospective studies and 14 were retrospective studies (table 1). Two retrospective studies compared PCI strategies between matched populations.[15,25] Five studies compared all 3 PCI strategies,[13-17] 10 studies compared Culprit-PCI vs. MV-PCI,[18-27] 2 studies Culprit-PCI vs. Staged-PCI,[28,29] and 1 study MV-PCI vs. Staged-PCI.[30]
In the majority of the studies MVD was defined as a significant stenosis in ≥1 major epicardial vessel or side branch, but in 2 studies a left main stenosis was also defined as two vessel disease.[26,27] Significant was defined as ≥70% stenosis, except for 2 studies that used ≥50%.[25,26]
The timing of staged procedures was in the majority of the studies during hospitalization or within 1 months after index PCI (table 1). Details about the quality of included prospective and retrospective studies are given in table 2 and 3. Six out of 14 retrospective studies were subanalyses of prospective registries. In addition, details are given regarding the studies in which planned staged procedures were allowed in patients treated according the Culprit-PCI strategy. Assessment of funnel plots suggested no publication bias.
Analyses were performed on short- and long-term mortality. Available evidence for the primary endpoint short-term mortality in pairwise and network comparisions is shown in Figure 2. A proper analysis on the secondary endpoints reinfarction, any revascularization, major bleeding and stroke was not possible because data was only available in a minority of the studies. Several authors provided additional information and outcome data.

Rate of the three PCI strategies across cohort studies

In cohort studies (total 37,436 pts)[14-17,20,21] providing rates of all 3 PCI strategies for MVD in their populations, Culprit-PCI was always the preferred treatment strategy (30,260/37,436 pts, 80.8%) as compared with MV-PCI (3,887/37,436 pts, 10.4%) and Staged-PCI (3,289/37,436 pts, 8.8%).

Baseline differences between the three PCI strategies

A summary of baseline variables for each included study group are detailed in table 4. In addition, summaries of baseline mean/percentages are given for studies included in each pairwise analysis. In studies comparing Culprit-PCI vs. MV-PCI, patients treated according to Culprit-PCI were older (62.3 vs. 60.7yr) and had higher rates of three vessel disease (32.5 vs. 28.8%). No differences were observed regarding sex (male, 72.7 vs. 73.0%), diabetes (23.0 vs. 22.4%) and cardiogenic shock (9.4 vs. 10.2%).

The pairwise analyses

Short-term mortality

Pooled short-term outcome data are detailed in Figure 3A-C. The Staged-PCI strategy was superior in both the comparison with Culprit-PCI (OR 3.03, 95%CI 1.41-6.51, p=0.005), and MV-PCI (OR 5.31, 95%CI 2.31-12.21, p<0.0001). In addition, mortality was lower in patients treated according to the Culprit-PCI strategy as compared with MV-PCI (OR 0.66, 95%CI 0.48-0.89, p=0.007). Only in the pairwise analysis of Culprit-PCI vs. MV-PCI, signs of heterogeneity were found across the trials (I^2=47%).

Two studies investigated Culprit-PCI versus MV-PCI in patients presenting in cardiogenic shock.[20,26] A total of 3248 patients were included, of which 470 (14.4%) were treated according to the MV-PCI strategy. Short-term mortality was in both studies lower in patients treated according to the Culprit-PCI strategy (total effect: OR 0.68; 95%CI 0.56-0.84, p=0.0003).

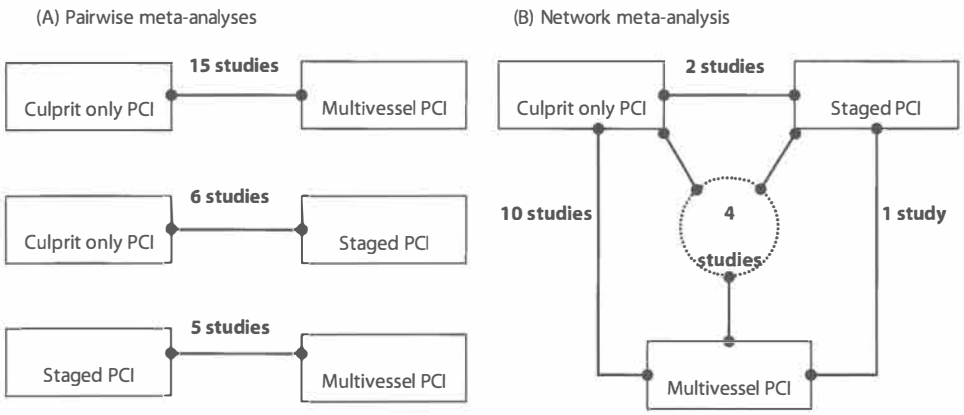

Figure 2. Evidence for primary endpoint short-term mortality in pairwise(A) and netwok(B) meta-analyses.

Table 2. Quality of prospective studies

Prim author, publication	RCT	Power calculation	Blinded assessment of angiographic data	Adjucation of adverse events	ITT-analysis	Definition of culprit-PCI regarding staged procedures	Completeness of survival data
Di Mario,2004	Yes	Yes	Yes	No	n/a	Staged procedures allowed	100%
Ochala,2004	Yes	No	Yes	No	n/a	No staged procedures allowed	100%
Politi,2010	Yes	Yes	No	No	Yes	No staged procedures allowed	mean follow-up used

ITT=intention-to-treat, n/a=data not available.

Table 3. Quality of retrospective studies

Prim author, publication	Control for confounders	Blinded assessment of angiographic data	Preferred PCI strategy	Definition of culprit-PCI regarding staged procedures	Completeness of survival data
Cavender,2009	± (Subanalysis of prospective registry)	-	n/a	No staged procedures allowed	n/a
Corpus,2004	-	-	Operator decision	No staged procedures allowed	100%
Dziewier,2010	± (Subanalysis of prospective registry)	-	n/a	No staged procedures allowed	100%
Han,2008	-	-	Operator decision	No staged procedures allowed	99.5%
Hannan,2010*	± (Subanalysis of prospective registry)	-	n/a	No staged procedures allowed	n/a
Kong,2006	± (Subanalysis of prospective registry)	-	Operator decision	n/a	n/a
Mohamad,2010	-	-	n/a	No staged procedures allowed	n/a
Poyen,2003	-	-	Multivessel PCI	Staged procedures allowed	98.8%
Qarawani,2008	-	-	Operator decision	Staged procedures allowed	n/a
Rigattieri,2007	-	-	Operator decision	No staged procedures allowed	95.5%
Roe,2001	-	-	Operator decision	Staged procedures allowed	100%
Schaaf,2010	-	-	n/a	n/a	n/a
Toma,2010	± (Subanalysis of prospective study)	-	n/a	n/a	99.7
Varani,2008	± (Subanalysis of prospective registry)	-	Operator decision	No staged procedures allowed	95.0%

+ =issue properly addressed, ± =issue possibly source of bias, - =issue likely to be source of bias, n/a=data not available.

Long-term mortality

Pooled long-term outcome data are detailed in Figure 4A-C. Also at long-term follow-up Staged-PCI was associated with significant lower mortality rates as compared with culprit-PCI, and MV-PCI. No significant heterogeneity was observed across trials.

Table 4. Baseline characteristics of included studies

	Age,mean			Male,%			Diabetes,%			Three vessel disease,%			Shock,%		
Strategy	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI
Prospective studies															
Di Mario,2004	65.3	53.5	-	84.6	88.2	-	41.2	11.5	-	47.1	30.8	-	Excl	Excl	-
Ochala,2004	-	65.0	67.0	-	72.9	75.0	-	31.3	34.1	-	n/a	n/a	-	Excl	Excl
Politi,2010	66.5	64.5	64.1	76.2	76.9	80.0	23.8	13.8	18.5	25.0	29.2	44.6	Excl	Excl	Excl
Khattab,2008	65.0	69.0	-	77.8	75.0	-	15.6	7.1	-	48.9	60.7	-	4.4	3.6	-
Retrospective studies															
Cavender,2009	62.0†	60.0†	-	72.1	71.5	-	23.4	24.7	-	n/a	n/a	-	10.3	13.8	-
Corpus,2004	63.0	n/a	n/a	69.2	n/a	n/a	17.0	n/a	n/a	n/a	n/a	n/a	3.4	n/a	n/a
Dziewier,2010	n/a	n/a	-	n/a	n/a	-	n/a	n/a	-	36.5	31.4	-	n/a	n/a	-
Han,2008	61.0	-	60.0	79.9	-	78.5	33.6	-	33.3	16.1	-	18.3	Excl	-	Excl
Hannan,2010*	n/a	n/a	n/a	78.7	75.0	84.2	n/a	n/a	n/a	26.4	25.7	42.1	Excl	Excl	Excl
Kong,2006	62.0	60.0	-	72.1	77.2	-	20.5	16.8	-	n/a	n/a	-	Excl	Excl	-
Mohamad,2010	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Poyen,2003	n/a	n/a	-	n/a	n/a	-	n/a	n/a	-	40.7	14.0	-	Excl	Excl	-
Qarawani,2008	67.0	66.0	-	64.0	65.3	-	16.0	12.6	-	44.0	43.2	-	Excl	Excl	-
Rigattieri,2007	68.0	-	64.8	69.6	-	79.7	32.6	-	15.6	47.8	-	29.7	Excl	-	Excl
Roe,2001	63.0†	64.0†	-	65.8	77.2	-	29.1	37.2	-	n/a	n/a	-	27.8	27.8	-
Schaaf,2010	n/a	n/a	-	n/a	n/a	-	n/a	n/a	-	n/a	n/a	-	100	100	-
Toma,2010	64.0†	64.0†	-	79.4	77.4	-	20.0	11.5	-	31.8	25.8	-	1.2	1.8	-
Varani 2008	79.8	68.7	67.1	75.0	67.4	67.7	n/a	n/a	n/a	34.0	35.4	46.9	6.4	15.0	4.2
Summary of baseline mean/percentage for studies included in each pairwise analysis															
	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI	Culprit-PCI	MV-PCI	Staged-PCI
Culprit vs. MV-PCI	62.3	60.7	-	72.7	73.0	-	23.0	22.4	-	32.5	28.8	-	9.4	10.2	-
Culprit vs. Staged-PCI	69.5	-	63.9	77.6	-	79.6	30.5	-	23.9	27.0	-	38.0	2.7	-	2.1
MV vs. Staged-PCI	-	67.0	66.1	-	73.6	79.3	-	21.2	24.8	-	28.0	43.6	-	2.9	0.9

*Different matched populations are used in the pairwise comparisons. †=median instead of mean. Excl=excluded from analysis, n/a= not available or analyzed.

The network analysis

All models had adequate convergence. There was no significant inconsistency in either short-term mortality (p=0.94 in the inconsistency model, p=0.75 in the node-splitting model and similar deviance information criteria for all three models) or long-term mortality (p=0.90 in the inconsistency model, p=0.78 in the node-splitting model and similar deviance information criteria for all three models).

Posterior means and 95% credibility intervals for the relative effects (OR) are shown for each comparison and both short- and long-term mortality in Figure 3 and 4.
In addition, the rank-probability of the 3 PCI strategies was investigated. This analysis demonstrated that for the primary endpoint short-term mortality the Staged-PCI strategy had a 0.9998 probability of being the best treatment as compared with Culprit-PCI (second rank probability of 0.94) and MV-PCI (third rank probability of 0.94). For long-term mortality, the rank-probability analysis also demonstrated that Staged-PCI had 0.995 probability of being the best treatment as compared with Culprit-PCI (second rank probability of 0.990) and MV-PCI (third rank probability of 0.996).

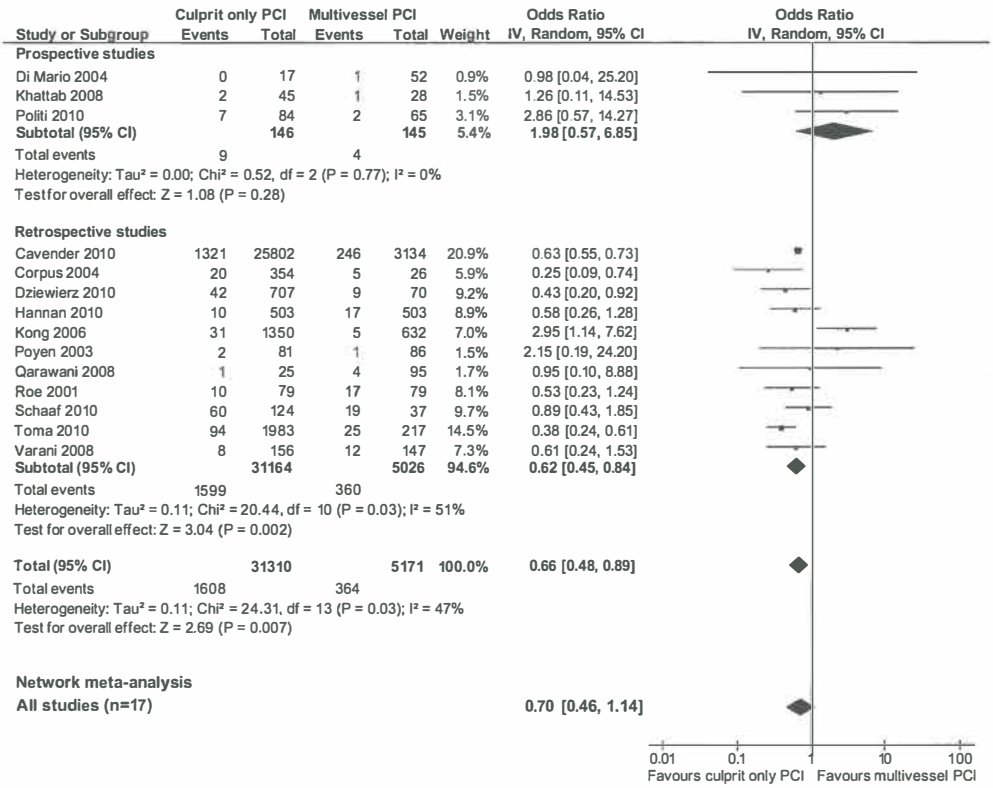

Figure 3A. Results of pairwise and network meta-analyses of studies comparing Culprit-PCI vs. MV-PCI for short-term mortality

DISCUSSION

This meta-analysis supports current guidelines advising to perform primary PCI for STEMI confined to the culprit vessel only. MV-PCI should be discouraged and significant non-culprit vessel lesions should only be treated during planned staged procedures.
Although considered safe, PCI remains associated with potential serious procedural complications, such as restenosis, stent-thrombosis and contrast-induced nephropathy.[3,4]

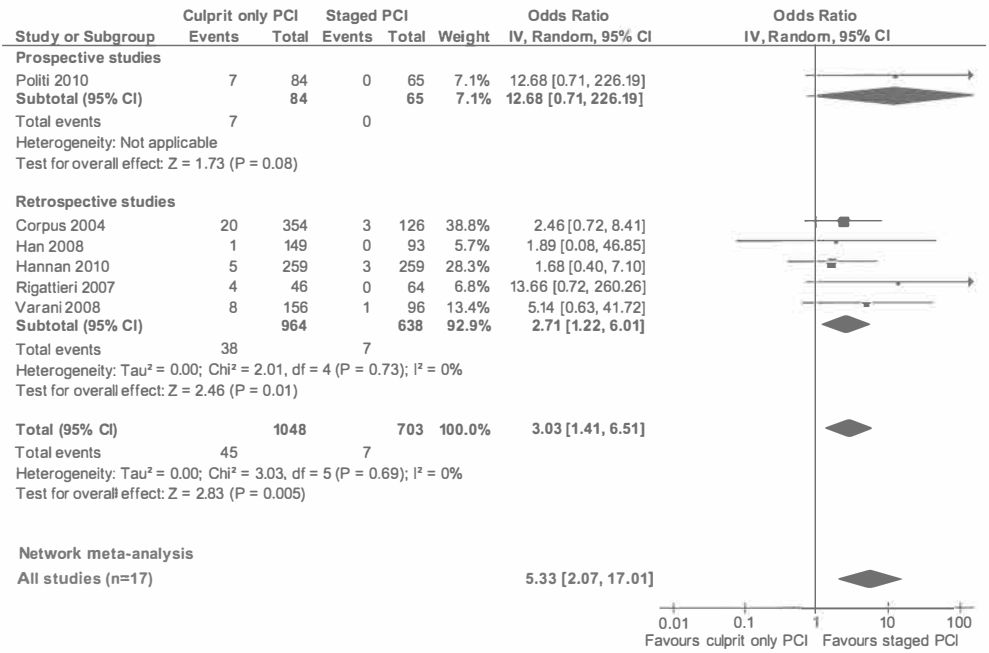

Figure 3B. Results of pairwise and network meta-analyses of studies comparing Culprit-PCI vs. Staged-PCI for short-term mortality

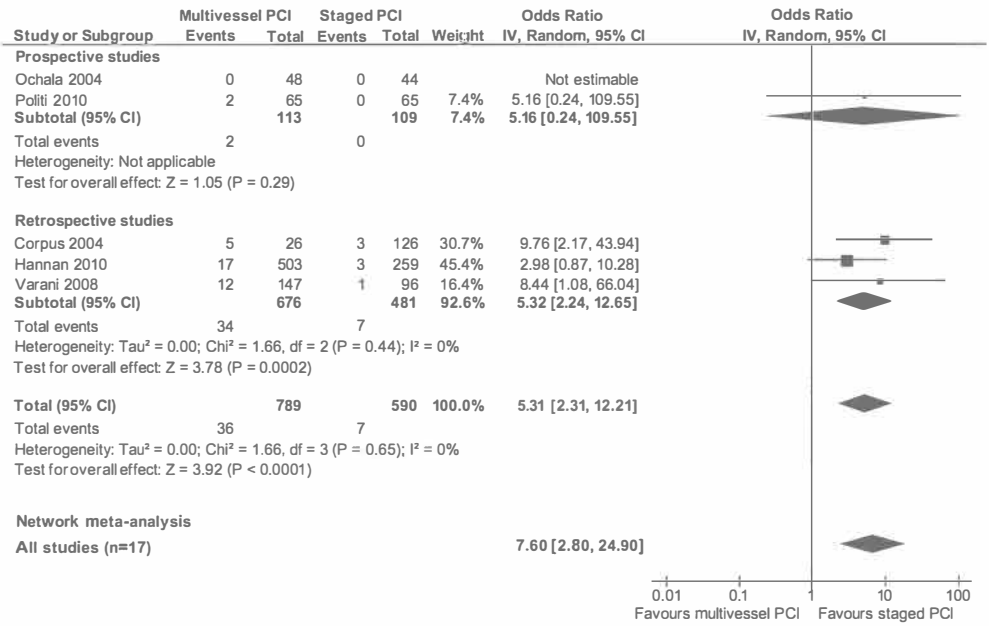

Figure 3C. Results of pairwise and network meta-analyses of studies comparing MV-PCI vs. Staged-PCI for short-term mortality

International guidelines therefore recommend using PCI selectively in those cases in which the benefit of a revascularization outweighs the risk of complications. For elective PCI extensive research has resulted in the consensus that it should be performed selectively in significant coronary lesions that cause myocardial ischemia.[3,4] For lesions that do not induce ischemia, the benefit of revascularization is less clear. In these patients an initial conservative medical strategy is likely to be as effective.[3,4,33] For lesions that do not induce ischemia, the benefit of revascularization is less clear. In these patients an initial conservative medical strategy is likely to be as effective. Current guidelines indicate that MV-PCI should not be performed in hemodynamic stable STEMI patients.[3,4] Only in patients with cardiogenic shock, PCI maybe recommended in all critically stenosed large epicardial coronary arteries. However, no randomized data have been published indicating that MV-PCI is beneficial in cardiogenic shock patients. Because of limited evidence on this subject, different opinions exist on the use of MV-PCI for STEMI across centers and operators. This is illustrated by a recent analysis of the NCDR database, which found incidences of MV-PCI ranging between 0 up to 38% in some participating centers.[20] One potential source of this variability may be the result of the operator considering that there were multiple infarct related artery lesions/arteries.

It has been hypothesized that in selected STEMI patients (e.g. cardiogenic shock) PCI of non-culprit vessel in the acute phase is able to reduce (border zone) ischemia and improve survival.[31,32] In addition, when more than on culprit lesion is suspected, multivessel PCI may also beneficial.[1] Multivessel PCI may also be more convenient for the patient as no secondary procedures are necessary. Further, there are logistic and economic reasons to perform multivessel PCI as it may limit staged procedures, reduces length of hospital stays and thereby medical costs. However, the present meta-analysis found that multivessel PCI during the acute phase of STEMI was associated with higher mortality rates as compared with culprit only or staged PCI. A small subanalysis in cardiogenic shock patients also did not show any mortality benefit of a multivessel PCI strategy in these patients.

These results indicate that the possible benefits of multivessel PCI do not outweigh the adverse effects associated with this aggressive strategy. These adverse effects are likely to be explained by the following factors.

First, the enhanced thrombotic and inflammatory environment of STEMI contributes to a higher risk of procedural complications as compared with elective procedures.[34-38] Factors that increase that risk are related to the complexity and duration of the procedure, which is the case with multivessel PCI for STEMI. Although a secondary staged PCI may also relate to an increased risk of complications, our results indicate that the risk associated with a secondary staged PCI is lower than an acute PCI.

Second, when performing multivessel PCI of significant non-culprit vessel, the PCI will be performed without objective evidence for the presence of myocardial ischemia. As the actual significance of a stenosis may be difficult to determine due to several factors in the acute phase of STEMI,[38,39] routine multivessel PCI of non-culprit vessel lesions can result in PCI of clinical irrelevant lesions. The benefit of not treating non-culprit vessel lesions during the acute phase, is that coronary angiograms can be discussed within a joint heart team to determine the best strategy for each individual patient.[3,4] In case of intermediate lesions, additional non-invasive ischemia tests and fractional flow reserve measurements can be performed before deciding to perform additional revascularizations.[3,4,40]

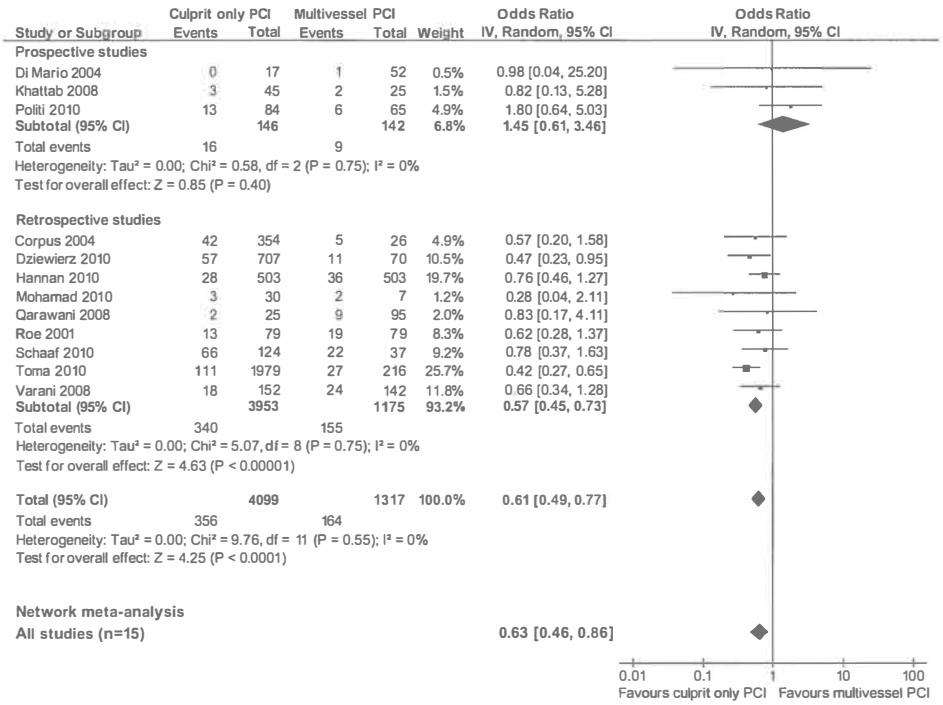

Figure 4A. Results of pairwise and network meta-analyses of studies comparing Culprit-PCI vs. MV-PCI for long-term mortality

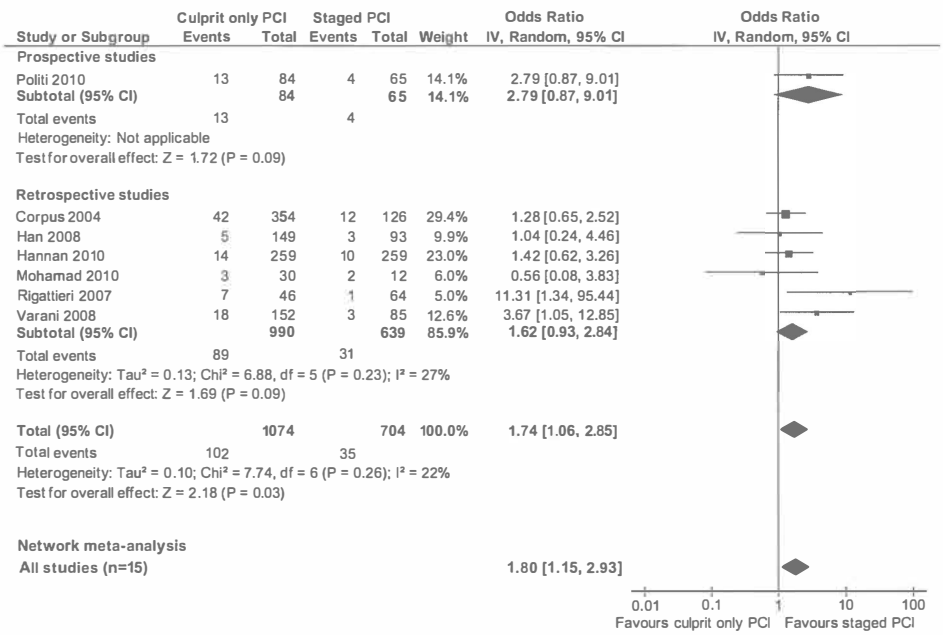

Figure 4B. Results of pairwise and network meta-analyses of studies comparing Culprit-PCI vs. Staged-PCI for long-term mortality

Limitations

Because of limited randomized data, this meta-analysis included both prospective and retrospective studies. As a consequence, the majority of the included studies were retrospective cohort analyses. The inclusion of studies with different designs and retrospective studies is likely to have induced heterogeneity in the results, as illustrated by the differences found between prospective and retrospective studies. Further, in most studies the operator's intent to perform one of the three PCI strategies was not prospectively registered and may be influenced by important patient characteristics for which we were not able to adjust. The results and conclusions should be interpreted with these limitations in mind. However, we have carried out a network analyses to assess the robustness of our findings and combining direct and indirect evidence about the three strategies. In this analysis, Staged-PCI was also consistently associated with significant lower mortality rates at both short- and long-term follow-up as compared with Culprit-PCI and MV-PCI. Only the comparison between Culprit-PCI and MV-PCI for short-term mortality lost significance. Additional analyses demonstrated that this was not due to the indirect comparisons, but due to the fact that the direct comparison in the network analysis was performed according to the Bayesian instead of the DerSimonian and Laird method.

Furthermore, the analyses between Culprit-PCI and MV-PCI in the included studies were primarily focused on the index PCI procedure. Therefore in some studies also staged PCI was allowed in the Culprit-PCI group. This may have influenced the results; however only the Culprit-PCI vs. MV-PCI and not the other pairwise comparisons. In addition, when

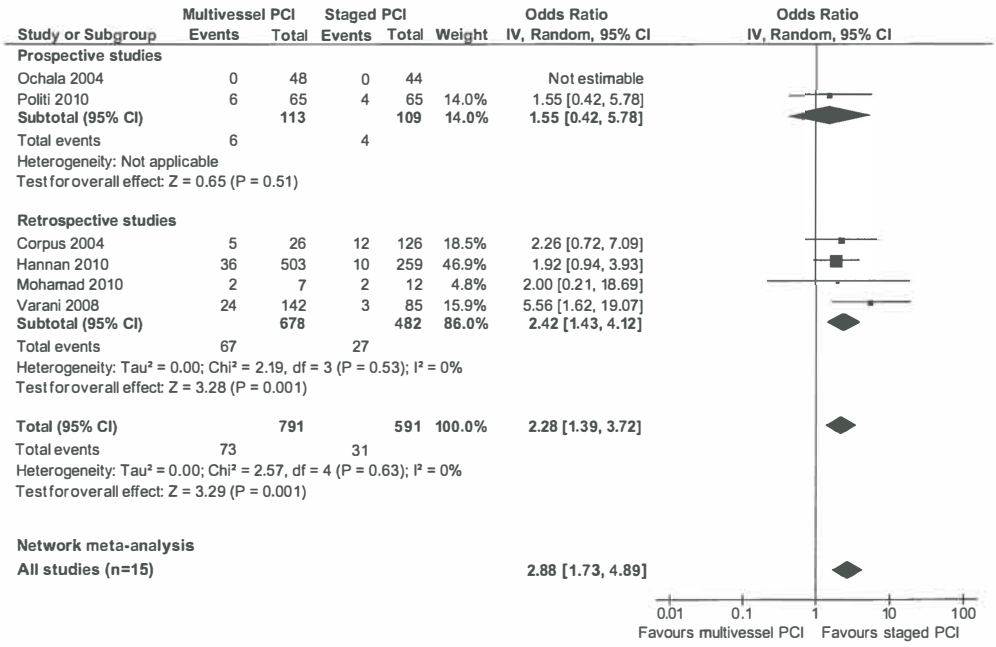

Figure 4C. Results of pairwise and network meta-analysis of studies comparing MV-PCI vs. Staged-PCI for long-term mortality

excluding studies who allowed staged PCI procedures or did not provide information on this, still a significant short term mortality benefit of Culprit-PCI over MV-PCI was observed. Finally, the role of timing of staged PCI procedures, CABG, and use of non-invasive ischemia testing in the management of MVD were not investigated nor discussed in the majority of the studies.

In conclusion, this meta-analysis supports current guidelines discouraging performance of multivessel primary PCI for STEMI. When significant non-culprit vessel lesions are suitable for PCI, they should only be treated during staged procedures. More prospective research should be performed to investigate which strategy is superior, in both hemodynamic stable and unstable STEMI patients (CABG vs. Culprit-PCI vs. Staged-PCI vs. MV-PCI). We therefore propose a prospective international registry to investigate these strategies. To facilitate intention-to-treat comparisons between the different strategies for multivessel PCI, this registry should focus on registering the operator's intent to perform one of the strategies at the time of the initial PCI.

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CHAPTER 5

Thrombus Aspiration during Primary Percutaneous Coronary Intervention

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ABSTRACT

Background

Primary percutaneous coronary intervention (PCI) is effective in opening the infarctrelated artery in patients with myocardial infarction with ST-segment elevation. However, the embolization of atherothrombotic debris induces microvascular obstruction and diminishes myocardial reperfusion.

Methods

We performed a randomized trial assessing whether manual aspiration was superior to conventional treatment during primary PCI. A total of 1071 patients were randomly assigned to the thrombus-aspiration group or the conventional-PCI group before undergoing coronary angiography. Aspiration was considered to be successful if there was histopathological evidence of atherothrombotic material. We assessed angiographic and electrocardiographic signs of myocardial reperfusion, as well as clinical outcome. The primary end point was a myocardial blush grade of 0 or 1 (defined as absent or minimal myocardial reperfusion, respectively).

Results

A myocardial blush grade of 0 or 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% of those in the conventional-PCI group (P<0.001). Complete resolution of ST-segment elevation occurred in 56.6% and 44.2% of patients, respectively (P<0.001). The benefit did not show heterogeneity among the baseline levels of the prespecified covariates. At 30 days, the rate of death in patients with a myocardial blush grade of 0 or 1, 2, and 3 was 5.2%, 2.9%, and 1.0%, respectively (P = 0.003), and the rate of adverse events was 14.1%, 8.8%, and 4.2%, respectively (P<0.001). Histopathological examination confirmed successful aspiration in 72.9% of patients.

Conclusions

Thrombus aspiration is applicable in a large majority of patients with myocardial infarction with ST-segment elevation, and it results in better reperfusion and clinical outcomes than conventional PCI, irrespective of clinical and angiographic characteristics at baseline. (Current Controlled Trials number, ISRCTN16716833.)

INTRODUCTION

Acute myocardial infarction with ST-segment elevation is caused by the rupture or erosion of an atherosclerotic plaque, initiating intraluminal thrombosis resulting in partial or complete occlusion of a coronary artery. [1-3] Primary percutaneous coronary intervention (PCI) is the preferred treatment for myocardial infarction with ST-segment elevation and is effective in opening the infarct-related artery.[4-6] However, microvascular obstruction with diminished myocardial perfusion occurs in a large proportion of patients with a patent epicardial vessel after primary PCI, and this event is associated with an increased infarct size, reduced recovery of ventricular function, and increased mortality.[7-11]

Microvascular obstruction is related to the embolization of plaque or thrombotic material downstream in the infarct-related artery.[12,13] Embolization can occur spontaneously or by means of mechanical fragmentation during PCI.[12-15] One coronary angiographic technique used to assess perfusion in the myocardial tissue is myocardial blush grading.[7,9,11] In clinical practice, electrocardiographic (ECG) analysis of the degree of resolution of ST-segment elevation after PCI is often used.[8,10,11]

The high frequency of suboptimal myocardial reperfusion after primary PCI has resulted in the development of various devices to protect the microcirculation.[16-24] A 6-French–compatible manualaspiration catheter is practical for this purpose, since it is relatively flexible and nontraumatic in use. Many previous trials have used findings on coronary angiography as selection criteria and have not performed a systematic analysis of the material retrieved during aspiration. We therefore evaluated the use of a manual-aspiration catheter to improve myocardial perfusion during primary PCI in patients with myocardial infarction with ST-segment elevation. Our patients were randomly assigned to a treatment group before coronary angiography was performed and therefore without consideration of angiographic selection criteria (such as the presence of a visible thrombus on angiography), and we conducted a histopathological analysis of the retrieved material as an additional evaluation of procedural efficacy.[25]

METHODS

Study Design and Population

The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) was a single-center, prospective, randomized, open trial involving the blinded evaluation of end points.[25] The institutional review board of the University Medical Center Groningen (Groningen, the Netherlands) approved the study. All patients provided written informed consent.

All consecutive patients presenting to the University Medical Center Groningen with a possible myocardial infarction with ST-segment elevation between January 2005 and December 2006 were considered eligible for participation. The inclusion criteria were symptoms suggesting acute myocardial ischemia lasting more than 30 minutes, the onset of symptoms less than 12 hours previously, and ST-segment elevation of more than 0.1 mV in two or more leads on the ECG. The exclusion criteria were the performance of a rescue PCI after thrombolysis, the known existence of a disease resulting in a life expectancy of less than 6 months, and the lack of informed consent.

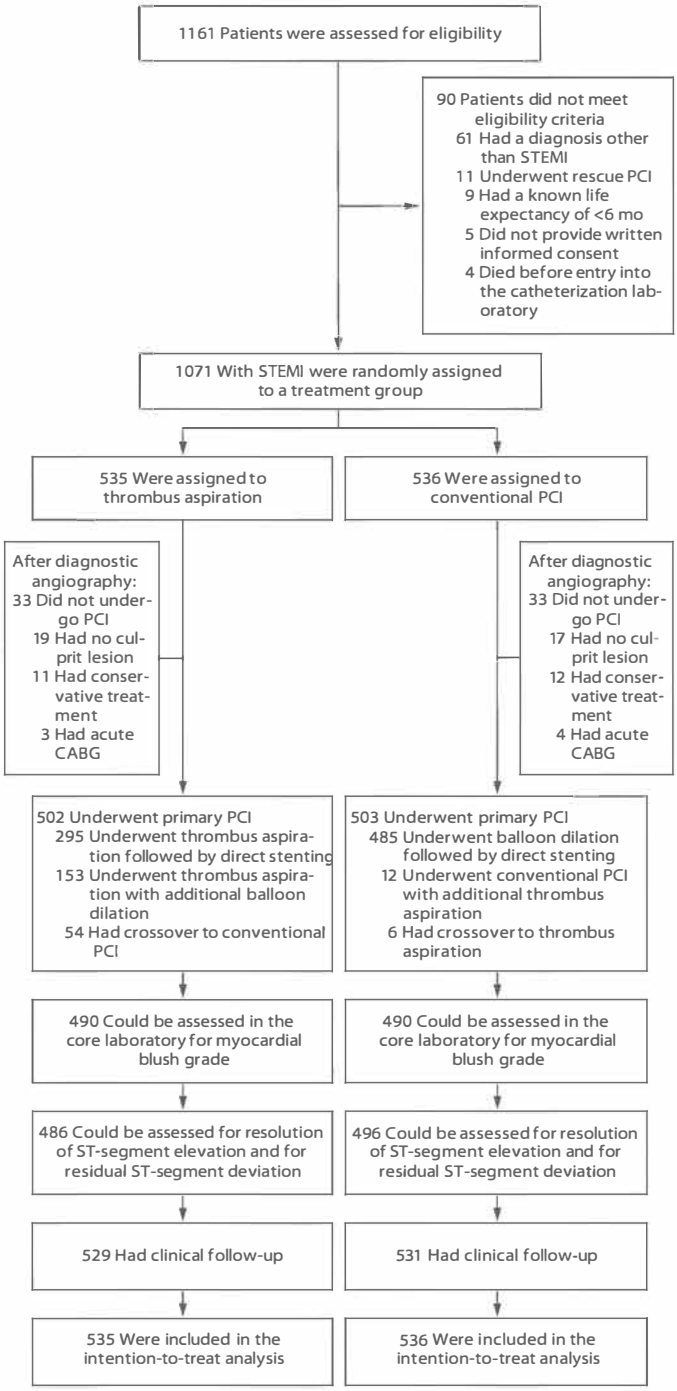


Figure 1. Trial flow diagram

Randomization and Treatment

Before diagnostic angiography was performed, patients were randomly assigned to undergo thrombus aspiration during PCI or conventional PCI, with the use of a computerized voice-response system. The randomization code was developed by means of a number generator used to select randomly permuted blocks of three to six patients, which were then stratified by the interventional cardiologist to achieve a balanced group assignment with regard to both the treatment group and the cardiologist performing the procedure.[25]

For all patients, the first procedural step was the passing of a floppy, steerable guidewire through the target lesion. In patients in the conventional-PCI group, this step was followed by balloon dilation to establish antegrade flow. In patients in the thrombus-aspiration group, this step was followed by the advancing of the 6-French Export Aspiration Catheter (Medtronic; crossing profile, 0.068 in.) into the target coronary segment during continuous aspiration; when necessary for stent delivery, balloon dilation was performed before stenting. In all patients, after the restoration of antegrade flow, intracoronary nitrates were given to ensure maximal epicardial vasodilation, in order to determine the size and length of the stent and to facilitate stent placement. All placed stents were bare-metal stents.

Pharmacologic treatment before PCI included the administration of aspirin (a loading dose of 500 mg), heparin (5000 IU), and clopidogrel (a loading dose of 600 mg). Patients also received the glycoprotein IIb/IIIa inhibitor abciximab, with the dose based on body weight, unless contraindicated, and additional heparin, with the dose based on the activated clotting time. Standard therapies after PCI included aspirin, clopidogrel, beta-blockers, lipid-lowering agents, and angiotensin-converting–enzyme inhibitors or angiotensin-II–receptor blockers, according to current guidelines.[6]

End Points, Assessment of Outcomes, and Definitions

The primary end point was the postprocedural frequency of a myocardial blush grade of 0 or 1 as detailed below.[25] Secondary end points were the postprocedural frequencies of a Thrombolysis in Myocardial Infarction (TIMI) flow grade of 3, complete resolution of ST-segment elevation, the absence of persistent ST-segment deviation, targetvessel revascularization, reinfarction, death, and the combination of major adverse cardiac events by 30 days after randomization.

Coronary angiography was performed before and after the PCI. TIMI flow grades were assessed as previously described.[26] Myocardial blush grades were assigned as previously described by Van 't Hof et al.[7]: 0, no myocardial blush; 1, minimal myocardial blush or contrast density; 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and 3, normal myocardial blush or contrast density, similar to that obtained during angiography of a contralateral or ipsilateral non–infarctrelated coronary artery. Persistent myocardial blush suggests leakage of contrast medium into the extravascular space and is given a grade of 0. Angiographic evidence of a thrombus was assessed according to the criteria summarized by Mabin et al.[27] Data from the coronary angiogram were analyzed at an independent core laboratory (Cordinamo). [25]

A 12-lead ECG was acquired at presentation and 30 to 60 minutes after PCI, and the ST-

Table 1. Baseline demographic, clinical and angiographic characteristics*

Characteristic	Thrombus aspiration (N=535)	Conventional PCI (N=536)	P-value
Clinical			
Age, yr	63±13	63±13	0.36
Male sex, N/total (%)	363/535 (67.9)	392/536 (73.1)	0.06
History, N/total (%)			
Hypertension	171/517 (33.1)	195/526 (37.1)	0.18
Diabetes mellitus	56/530 (10.6)	67/532 (12.6)	0.30
Hypercholesterolemia	115/485 (23.7)	130/480 (27.1)	0.23
Myocardial infarction	50/528 (9.5)	57/533 (10.7)	0.51
PCI	39/526 (7.4)	38/531 (7.2)	0.87
CABG	17/529 (3.2)	22/533 (4.1)	0.43
Cerebrovascular disease	17/517 (3.3)	21/522 (4.0)	0.53
Cerebrovascular disease in family	235/509 (46.2)	229/514 (44.6)	0.58
Current smoking, N (%)	213/463 (46.0)	225/469 (48.0)	0.57
Preinfarction angina	258/483 (53.4)	233/476 (48.9)	0.17
Total ischemic time, min			0.61
Median	190	185	
Interquartile range	110-270	107-263	
Body mass index †	27±4	27±4	0.69
Systolic blood pressure - mmHg	128±26	130±26	0.34
Diastolic blood pressure - mmHg	74±15	75±16	0.65
Heart rate - bpm	78±18	78±19	0.98
Angiographic			
N of diseased vessels, N/total (%)			0.84
0	13/533 (2.4)	10/534 (1.9)	
1	166/533 (31.1)	157/534 (29.4)	
2	175/533 (32.8)	174/534 (32.6)	
3	178/533 (33.4)	193/534 (36.1)	
Infarct related vessel, N/total (%)			0.62
left anterior descending artery	221/515 (42.9)	223/517 (43.1)	
left circumflex artery	93/515 (18.1)	79/517 (15.3)	
right coronary artery	189/515 (36.7)	204/517 (39.5)	
other	12/515 (2.3)	11/517 (2.1)	
TIMI flow, N/total (%)			0.23
0 or 1	288/526 (54.7)	316/531 (59.5)	

(Continued)

Table 1. Continued

Characteristic	Thrombus aspiration (N=535)	Conventional PCI (N=536)	P-value
2	102/526 (19.4)	85/531 (16.0)	
3	136/526 (25.9)	130/531 (24.5)	
Thrombus, N/total (%)	252/519 (48.6)	233/529 (44.0)	0.14
Procedural			
Door-to-balloon time, min			0.92
Median	28	26	
Interquartile range	14-42	12-40	
Duration of fluoroscopy, min			0.64
Median	7	7	
Interquartile range	4.5–9.5	4.5–9.5	
Administration of glycoprotein IIb/IIIa inhibitor, N/ total (%)	469/502 (93.4)	452/503 (89.9)	0.12
Stent implantation, N/total (%)	442/479 (92.3)	438/476 (92.0)	0.88
Length of stented segment, mm	18.5±8.7	18.6±8.9	0.48
Diameter of stented segment, mm	3.0±1.1	3.0±1.1	0.68
Intra-aortic balloon pump, N/total (%)	23/479 (4.8)	35/470 (7.4)	0.09
Postprocedural TIMI flow grade 3, N/total (%)	431/501 (86.0)	409/496 (82.5)	0.12
Intraprocedural complications, N/total (%)			
Side-branch occlusion	5/502 (1.0)	4/503 (0.8)	1.00
Flow-limiting dissections	0	0	1.00
Emergency CABG	1/502 (0.2)	1/503 (0.2)	1.00

Plus–minus values are means ±SD. Data for total ischemic time were available for 492 patients in the thrombus-aspirationgroup and 488 patients in the conventional percutaneous-coronary-intervention (PCI) group; for body-mass index, 488 and 490 patients, respectively; for systolic and diastolic blood pressures, 514 and 522; for heart rate, 512 and 522; for time from hospital entry to first balloon inflation or aspiration, 502 and 503; for duration of fluoroscopy, 490 and 495; and for length and diameter of stented segment, 479 and 476. CABG denotes coronary-artery bypass grafting, and TIMI Thrombolysis in Myocardial Infarction.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

segments on the postprocedural ECG were compared with those on the ECG at presentation. The degree of resolution of ST-segment elevation was categorized as complete (>70%), partial (30 to 70%), or none (<30%).[8] Persistent ST-segment deviation, defined as the sum of the ST-segment depression and the ST-segment elevation, was categorized as less than 2 mm, 2 to 10 mm, and more than 10 mm. The presence or absence of pathologic Q waves was also recorded.

Filtered, aspirated material was fixed in formalin for 24 hours. Histologic sections were cut and stained with hematoxylin and eosin for examination with a light microscope (magnification, ×100). Immunostaining was performed to optimize the visualization of smooth-muscle cells and macrophage foam cells. Aspiration was defined as effective or

not effective on the basis of the presence of atherothrombotic material in the aspirate samples. The material was classified as from a thrombus containing only platelets, a thrombus with an erythrocyte component, or a thrombus with plaque, as well as according to length: small (<0.5 mm), moderate (0.5 to 2 mm), or large (>2 mm).
Follow-up data at 30 days were obtained from hospital records and through telephone interviews. Major bleeding was defined as symptomatic bleeding in a critical area or organ, bleeding causing a decrease in hemoglobin level of 2.0 mmol or more per liter, or bleeding that led to blood transfusion. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of the levels of cardiac markers to at least twice the upper limit of the normal range. Target-vessel revascularization was defined as ischemia-driven revascularization of the infarct-related artery, performed by means of PCI or surgery (e.g., coronary-artery bypass grafting) during the follow-up period. A major adverse cardiac event was defined as death, reinfarction, or target-vessel revascularization.

Statistical Analysis

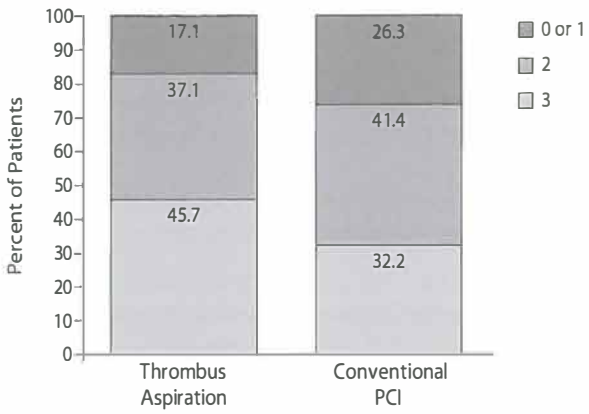
We estimated that we would have to enroll 1080 patients to achieve a power of 80%, with a twosided significance level of 0.05, to detect a 25% reduction in the primary end point in patients who underwent thrombus aspiration as compared with those who underwent conventional PCI, assuming a 30% rate of myocardial blush grade of 0 or 1 in the conventional-PCI group.[25] The study committee (see the Appendix) performed a planned interim analysis after 300 patients had been enrolled. The stopping limit was a difference of more than 25% in the primary end point between the two groups, with a P value of less than 0.01.
Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with the use of a two-tailed Student's t-test. Prespecified subgroup analyses were performed by means of logistic-regression analyses with formal tests for interaction.[28] We analyzed data for all patients who were randomly assigned to a treatment group and for whom outcome data were available. Exploratory analyses of the association between the surrogate and clinical end points were performed by means of logistic-regression analysis. Two-sided significance tests were used. P values of less than 0.05 were considered to indicate statistical significance. SPSS software, version 12.0.1, was used in all statistical analyses.
Data management and statistical analyses were performed by staff of the data coordinating center (see the Appendix) and the principal investigator, who vouches for the accuracy and completeness of the data.

RESULTS

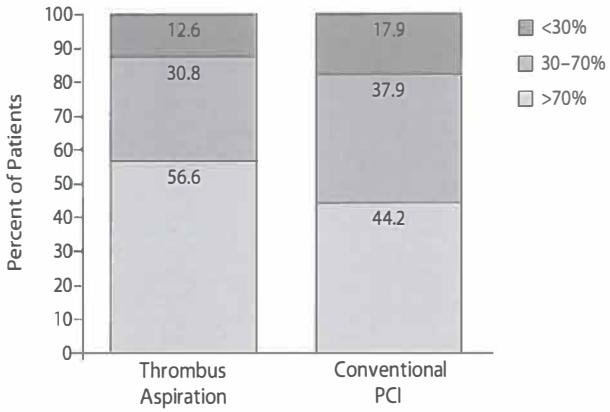
Study Population

During the study period, 1161 patients were considered for inclusion, and 1071 patients were enrolled according to the eligibility criteria (Fig. 1). Before coronary angiography, patients were randomly assigned to undergo either thrombus aspiration during PCI (535 patients) or conventional PCI (536 patients). The baseline clinical and angiographic characteristics were similar in the two groups (Table 1).

A Myocardial Blush Grade



B Resolution of ST-Segment Elevation



C Persistent ST-Segment Deviation

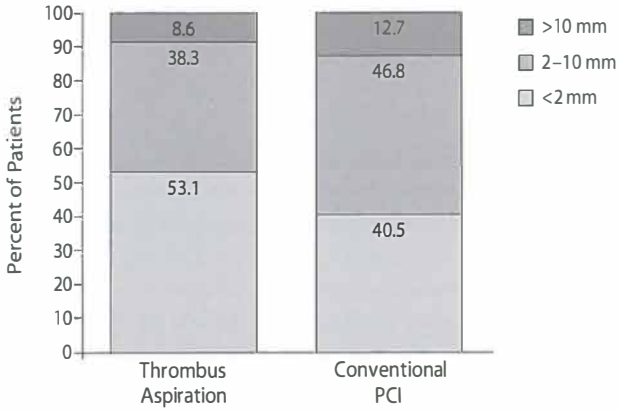


Figure 2. Myocardial Reperfusion Data on Angiography and Electrocardiography, According to Treatment Group.
The percentages of patients are shown according to myocardial blush grade on the angiogram (A) and the degree of resolution of ST-segment elevation (B) and persistent ST-segment deviation (C) on the electrocardiogram. PCI denotes percutaneous coronary intervention.

Procedural Data

On the basis of the initial angiographic findings, 33 patients (approximately 6%) in each group did not undergo PCI. In the thrombus-aspiration group, aspiration and direct stent implantation were performed in 295 patients (55.1%), balloon dilation was performed before stent implantation in 153 patients (28.6%), and conventional PCI was performed in 54 patients (10.1%) in whom the operator judged the target artery to be too small or too tortuous to permit use of the aspiration catheter (Fig. 1).

Data about the procedures and intraprocedural complications are shown in Table 1. None of the complications were thought to be related to the aspiration device used. There were no intraprocedural deaths or strokes.

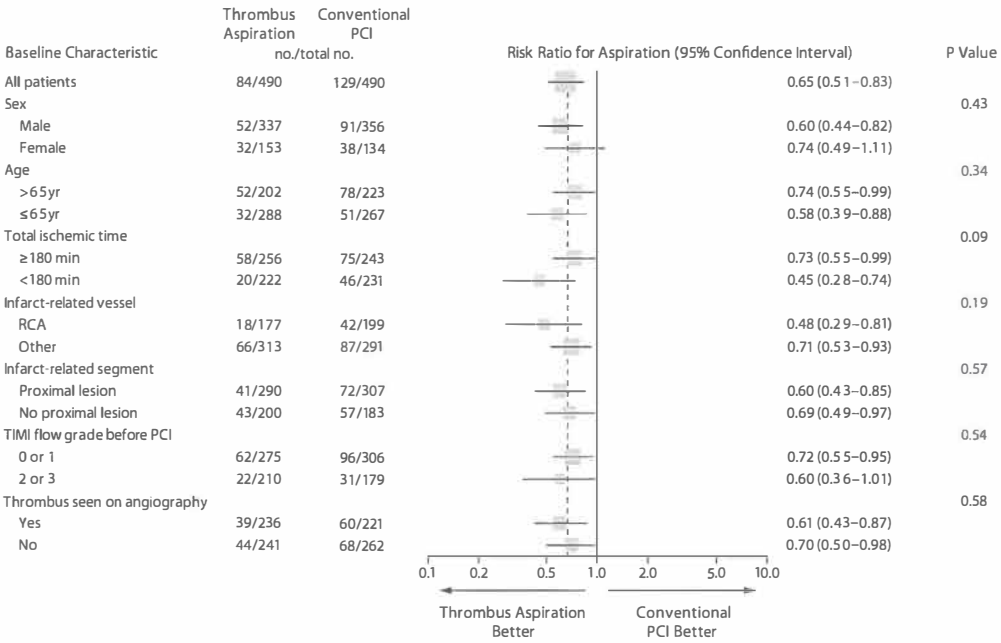


Figure 3. Risk Ratios for the Primary End Point, According to Prespecified Clinical or Angiographic Subgroup

Myocardial Reperfusion

The postprocedural myocardial blush grade could be assessed in 980 (490 in each group) of the 1005 patients (97.5%) who underwent PCI. A myocardial blush grade of 0 or 1 occurred in 84 of the 490 patients (17.1%) in the thrombus-aspiration group and in 129 of the 490 patients (26.3%) in the conventional-PCI group (risk ratio, 0.65; 95% confidence interval [CI], 0.51 to 0.83; P<0.001) (Fig. 2A).

The ECGs obtained at baseline and after the procedure were analyzed in 982 of the 1005 patients (97.7%) who underwent PCI. The median time from treatment to the postprocedural ECG was 44 minutes (interquartile range, 25 to 63) in the thrombus-aspiration group and 43 minutes (interquartile range, 25 to 61) in the conventional-PCI

group (P = 0.40). Complete ST-segment resolution occurred in 275 of the 486 patients (56.6%) in the thrombus-aspiration group and 219 of the 496 patients (44.2%) in the conventional-PCI group (risk ratio, 1.28; 95% CI, 1.13 to 1.45; P<0.001) (Fig. 2B). Similarly, 258 of the 486 patients (53.1%) in the thrombus-aspiration group had no persistent ST-segment deviation, as compared with 201 of the 496 patients (40.5%) in the conventional-PCI group (risk ratio, 1.31; 95% CI, 1.14 to 1.50; P<0.001) (Fig. 2C). In the thrombus-aspiration group, 119 of 486 patients (24.5%) did not have pathologic Q waves on the ECG, as compared with 79 of 496 patients (15.9%) in the conventional-PCI group (risk ratio, 1.54; 95% CI, 1.19 to 1.99; P = 0.001).
There was no evidence that the benefit with regard to the primary end point was heterogeneous among the baseline levels of the prespecified covariates. There were no significant interactions for any subgroups (Fig. 3).

Histopathological Features

Table 2 shows the rate of retrieval and the histopathological characteristics and size of the aspirate, according to initial angiographic findings in the patients who underwent aspiration. Histopathological examination was performed in 454 patients, which in 331 patients (72.9%) showed atherothrombotic material.

Clinical Outcome at 30 Days

In the thrombus-aspiration group and the conventional-PCI group, there was major bleeding in 20 of 529 patients (3.8%) and 18 of 531 patients (3.4%), respectively (risk ratio, 1.11; 95% CI, 0.60 to 2.08; P = 0.11); death in 11 of 529 (2.1%) and 21 of 531 (4.0%) (risk ratio, 0.52; 95% CI, 0.26 to 1.07; P = 0.07); reinfarction in 4 of 529 (0.8%) and 10 of 531 (1.9%) (risk ratio, 0.40; 95% CI, 0.13 to 1.27; P = 0.11); target-vessel revascularization in 24 of 529 (4.5%) and 31 of 531 (5.8%) (risk ratio, 0.77; 95% CI, 0.46 to 1.30; P = 0.34); and major adverse cardiac events at 30 days in 36 of 529 (6.8%) and 50 of 531 (9.4%) (risk ratio, 0.72; 95% CI, 0.48 to 1.08; P = 0.12). The rates of death and major adverse cardiac events at 30 days were both significantly related to myocardial blush grade, resolution of ST-segment elevation, and ST-segment deviation (P = 0.003 for the association between death and myocardial blush grade; P<0.001 for all other associations) (Fig. 4).

DISCUSSION

The results of our randomized trial show that effective manual aspiration of atherothrombotic material is feasible in a large majority of patients presenting with myocardial infarction with STsegment elevation. As compared with balloon angioplasty as an initial step in primary PCI, aspiration before stenting results in improved myocardial reperfusion, documented by a clear improvement in the myocardial blush grade, increased resolution of ST-segment elevation, and reduced residual ST-segment deviation. This beneficial effect of aspiration was consistently present in all patients, irrespective of baseline clinical or angiographic characteristics such as age, sex, infarctrelated coronary artery, preprocedural TIMI flow, or visible thrombus on the angiogram. Atherothrombotic material was retrieved in 73% of the patients who underwent thrombus aspiration, and

the main constituent of the retrieved material was platelets.

Our data confirm the prognostic value of the myocardial blush grade and degree of resolution of the ST-segment elevation after reperfusion therapy, since these variables were strongly related to the 30-day rates of death and major adverse cardiac events.[7,8] The trends we found for these rates were expected from the differences between the two groups in variables reflecting myocardial reperfusion. Since a larger proportion of patients in the thrombus-aspiration group than in the conventional-PCI group did not have pathologic Q waves on the postprocedural ECG, this benefit may be mediated, at least in part, by myocardial salvage.

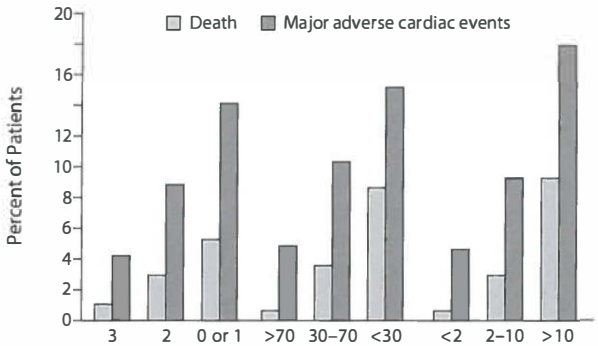
Table 2. Histopathological characteristics of coronary-artery thrombi from initial findings on coronary angiography in patients undergoing thrombus aspiration*

	Patients,	Infarct-Related Vessel				TIMI Flow Grade		Thrombus seen	
Characteristic	N	LAD	Cx	RCA	Other	0 or 1	2 or 3	Yes	No
Total patients, N	454	201	75	171	7	265	185	225	217
Aspirate collected, N (%)	331 (72.9)	138 (68.7)	49 (65.3)	140 (81.9)	4 (57.1)	201 (75.8)	127 (68.6)	173 (76.9)	146 (67.3)
Composition of aspirate									
Platelet, N (%)	224 (67.7)	101	33	88	2	120	101	116	100
<0.5 mm, %	70.5	72.3	72.7	67.0	100	68.3	74.3	67.2	76.0
0.5–2.0 mm, %	24.1	21.8	18.2	29.6	0	27.5	18.8	29.3	17.0
>2.0 mm, %	5.4	5.9	9.1	3.4	0	4.2	6.9	3.5	7.0
Erythrocyte, N (%)	50 (15.1)	14	8	26	2	45	5	32	15
<0.5 mm, %	4.0			7.7	0	4.4		6.3	
0.5–2.0 mm, %	22.0	42.9	25.0	11.5	0	24.4		18.7	33.3
>2.0 mm, %	74.0	57.1	75.0	80.8	100	71.2	100	75.0	66.7
Plaque, N (%)	57 (17.2)	23	8	26	0	36	21	25	31
<0.5 mm, %	33.3	39.1	25.0	30.8		30.6	38.1	28.0	38.7
0.5–2.0 mm, %	45.6	34.8	62.5	50.0		44.4	47.6	48.0	41.9
>2.0 mm, %	21.1	26.1	12.5	19.2		25.0	14.3	24.0	19.4

* The 454 patients undergoing thrombus aspiration were 448 patients in the thrombus-aspiration group and 6 patients in the conventional percutaneous-coronary-intervention group. Data are reported for the patients who had coronary angiographic data at baseline. "Platelet" was defined as a thrombus composed only of platelets, "erythrocyte" as a thrombus with bands of erythrocytes, and "plaque" as a thrombus with any fragment of vessel wall, cholesterol crystals, inflammatory cells, or collagen tissue. All millimeter measurements refer to length. Cx denotes left circumflex artery, LAD left anterior descending artery, and RCA right coronary artery.

The clinical importance of embolization of atherothrombotic material from unstable plaques in patients with myocardial infarction with ST-segment elevation has been recognized,[12,13] and embolic protection during PCI in such patients has been tested with various devices in small or medium-sized trials, with diverse results.[16-24] This variation in results may be in part related to the device used, since trials involving manual-aspiration devices have all shown favorable effects of aspiration on myocardial-perfusion

variables.[20-22] Most of the previous trials have enrolled patients who were selected on the basis of angiographic features,[16-19,21-24] since it was assumed that patients with a large thrombotic burden are identified on angiography and will particularly benefit from the treatment. Our data show that angiographic variables such as TIMI flow or the presence of a visible thrombus are not predictors of patients in whom aspiration will be effective. Our findings therefore support the concept that the presence of a thrombus plays an important role in the pathophysiological characteristics of most patients with myocardial infarction with ST-segment elevation.



Rate of death (%)	1.0	2.9	5.2	0.7	3.6	8.6	0.6	3.0	9.3
Rate of major adverse cardiac events (%)	4.2	8.8	14.1	4.8	10.3	15.2	4.7	9.2	18.0

Figure 4. Rates of Death and Major Adverse Cardiac Events, According to Myocardial Blush Grade and ST-Segment Variables

We powered our trial on the assumption of a 25% reduction in the frequency of myocardial blush grade of 0 or 1 in the thrombus-aspiration group. Our data confirm a benefit of this magnitude, albeit with a somewhat lower incidence of myocardial blush grade of 0 or 1 in the conventional-PCI group than expected: 26.4% instead of 30%. This may be explained by the administration of pharmacotherapy immediately after the diagnosis of myocardial infarction with ST-segment elevation was made, followed by the use of abciximab at the start of the PCI procedure. Our trial provides a systematic analysis of the role of coronary thrombi in a representative, contemporary population with myocardial infarction with ST-segment elevation, since aspiration was performed soon after the onset of symptoms in a large cohort of patients who were not selected on the basis of angiographic characteristics and were randomly assigned to a treatment group. The rate of retrieval of atherothrombotic material (73%) is somewhat lower than that reported in smaller, nonrandomized pathological thrombectomy studies of patients who had myocardial infarction with ST-segment elevation,[13,29] possibly because of the selection of patients and angiographic characteristics or differences in the devices and antithrombotic regimens used.

Our histopathological findings confirm earlier observations that thrombi predominantly composed of platelets are common in patients who have myocardial infarction with ST-segment elevation.[13,29,30] Platelets are thought to play an importantrole in embolization and microvascular dysfunction.[12,31] Mechanical removal of a thrombus before PCI reduces the existing source of embolization but does not address platelet aggregates generated after PCI. These can be abolished with the use of platelet inhibitors.[32] It is therefore possible that the combined use of aspiration and glycoprotein IIb/IIIa inhibitors will have a synergistic effect.

The platelet thrombi were mostly small or moderate in size, whereas the erythrocyte-rich thrombi were moderate or large in size. This may reflect the process whereby a platelet thrombus forms by means of the adherence and aggregation of platelets on a disrupted lesion, followed by the development of thrombus through the deposition of erythrocytes in the stagnant blood flow over the platelet thrombus.[1,33,34] The association between large erythrocyte-rich thrombi and a TIMI flow grade of 0 or 1 before PCI is consistent with this mechanism.

We could not identify atherothrombotic material in 27% of patients in whom aspiration was performed. This may be due to a variety of mechanisms. First, a thrombus may be dissolved by endogenic or pharmacologic antithrombotic or fibrinolytic agents. Second, a thrombus may break off and embolize before PCI or during PCI, owing to the guidewire or aspiration device. In some patients in our trial, mechanical resistance at the site of occlusion prevented passage of the aspiration device through the infarct-related segment. It seems likely that, in some patients who have myocardial infarction with ST-segment elevation, a high-grade, nonthrombotic, unstable atherosclerotic plaque causes the coronary obstruction (e.g., a plaque with hemorrhage).[33,34] The patients who did not have a response to aspiration might also not have shown reperfusion after thrombolytic therapy. Third, within hours after formation, a thrombus may be covered by mononuclear cells that stop the deposition of platelets.[35] Finally, fragile material may disintegrate while passing through the catheter or filter or in the collection bottle.

Our trial has several limitations. First, it represents a single-center experience using surrogate end points. However, the fact that the surrogate end points of myocardial blush grade and the electrocardiographic variables of reperfusion were clearly associated with the rates of death and major adverse cardiac events supports the validity of using such end points in studies of patients who have myocardial infarction with ST-segment elevation. Second, to prevent selection bias, we performed randomization before coronary angiography. As a consequence, some patients did not undergo PCI or received the alternative therapy. This may have diluted to some extent the positive effects of aspiration, but it makes our findings applicable to a general population with myocardial infarction with ST-segment elevation. Third, it cannot be ruled out that extractable thrombi differ from thrombi in situ. Finally, it has been suggested that primary stenting without balloon predilation in patients who have myocardial infarction with ST-segment elevation results in improved distal flow and reduced embolization. Our study was not designed to evaluate the effect of dilation before stenting. This issue needs further investigation in a randomized setting.

In conclusion, we found that manual thrombus aspiration can be performed in a large majority of patients presenting with myocardial infarction with ST-segment elevation, irrespective of their clinical and angiographic features (e.g., a visible thrombus on angiography) and results in improved myocardial reperfusion and clinical outcome as compared with conventional PCI. The significant relationship we found between myocardial and electrocardiographic variables of reperfusion and the rates of death and major adverse cardiac events supports the validity of these reperfusion variables as surrogate end points in patients who have myocardial infarction with ST-segment elevation. The histopathological findings in the aspirate specimens underline the importance of antiplatelet therapy in improving the outcome after primary PCI.

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CHAPTER 6

Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study TAPAS) a 1-year follow-up study

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SUMMARY

Background

Percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction can be complicated byspontaneous or angioplasty-induced embolisation of atherothrombotic material. Distal blockage induces microvascular obstruction and can result in less than optimum reperfusion of viable myocardium. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) found that thrombus aspiration resulted in improved myocardial reperfusion compared with conventional PCI, but whether this benefit improves clinical outcome is unknown. We aimed to investigate whether the early efficacy of thrombus aspiration seen in TAPAS translated into clinical benefit after 1 year.

Methods

Patients with ST-elevation myocardial infarction enrolled at the University Medical Centre Groningen were randomly assigned in a 1:1 ratio to either thrombus aspiration or conventional treatment, before undergoing initial coronary angiography. Exclusion criteria were rescue PCI after thrombolysis and known existence of a concomitant disease with life expectancy less than 6 months. Of the 1071 patients enrolled between January, 2005, and December, 2006, vital status at or beyond 1 year after randomisation was available for 1060 (99%). The primary endpoint was cardiac death or non-fatal reinfarction after 1 year, and analysis was by intention to treat. The TAPAS trial is registered with Current Controlled Trials number ISRCTN16716833.

Findings

Cardiac death at 1 year was 3.6% (19 of 535 patients) in the thrombus aspiration group and 6.7% (36 of 536) in the conventional PCI group (hazard ratio [HR] 1.93; 95% CI 1.11–3.37; p=0.020). 1-year cardiac death or non-fatal reinfarction occurred in 5.6% (30 of 535) of patients in the thrombus aspiration group and 9.9% (53 of 536) of patients in the conventional PCI group (HR 1.81; 95% CI 1.16–2.84; p=0.009).

Interpretation

Compared with conventional PCI, thrombus aspiration before stenting of the infarcted artery seems to improve the 1-year clinical outcome after PCI for ST-elevation myocardial infarction. Funding Medtronic and the Thorax Centre of the University Medical Centre Groningen.

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion therapy for ST-elevation myocardial infarction. Spontaneous or PCI-induced embolisation of atherothrombotic material from the culprit lesion into the distal vasculature occurs in most patients. Distal blockage induces microvascular obs truction and can result in suboptimum reperfusion of viable myocardium.[1] In several randomised controlled trials, thrombus aspiration has improved myocardial reper fusion compared with conventional PCI.[2–6] The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)[2] found that thrombus aspiration resulted in improved myocardial reperfusion, indicated by the myocardial blush grade and ST-segment analysis on the 12-lead electrocardiogram (ECG), compared with conventional PCI. However, data from randomised trials that have assessed clinical outcomes are scarce, and several meta-analyses have shown conflicting results.[7,8] The aim of our study was to investigate whether the early efficacy of thrombus aspiration translates into clinical benefit after 1 year.

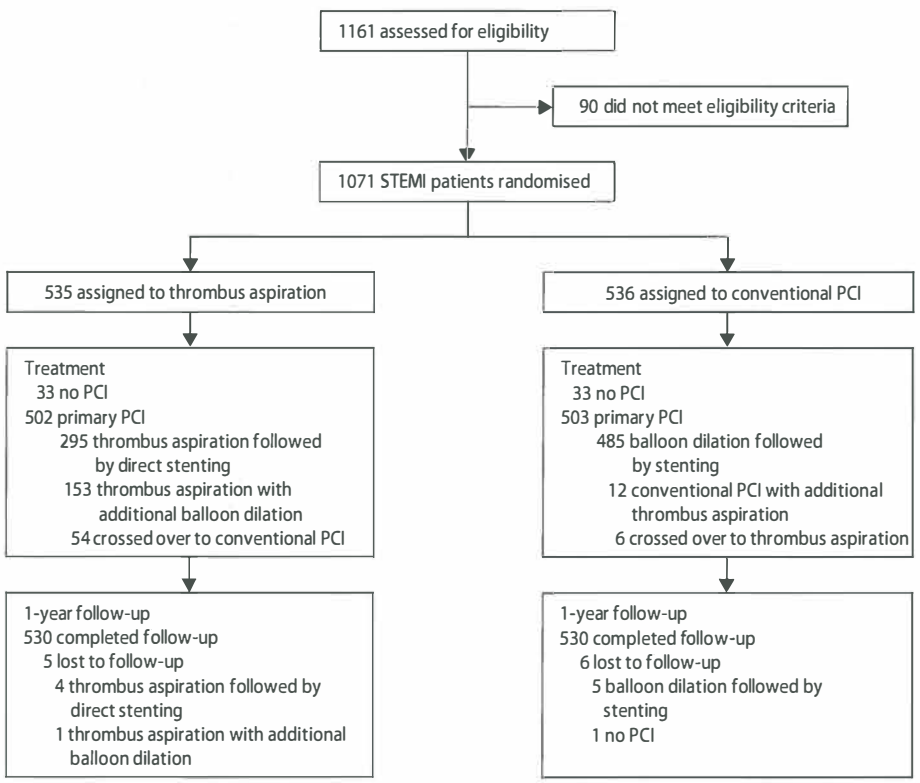


Figure 1. Trial profile

Table 1. Baseline clinical and angiographic characteristics

	Thrombus aspiration (N=535)	Conventional PCI (N=536)	P-value
Baseline characteristics			
Age in years, mean±SD	63±13	63±13	
Male sex, N/total (%)	363/535 (67.9)	392/536 (73.1)	
Risk factors, N/total (%)			
Diabetes	56/530 (10.6)	67/532 (12.6)	
Hypertension	171/517 (33.1)	195/526 (37.1)	
Hypercholesterolemia	115/485 (23.7)	130/480 (27.1)	
Previous myocardial infarction	50/528 (9.5)	57/533 (10.7)	
Previous PCI	39/526 (7.4)	38/531 (7.2)	
Previous CABG	17/529 (3.2)	22/533 (4.1)	
Family history	235/509 (46.2)	229/514 (44.6)	
Body mass index, mean ± SD	27±4	27±4	
Current smoking, N/total (%)	213/463 (46.0)	225/469 (48.0)	
Total ischemic time in min, median (IQR)	190 (110-270)	185 (107-263)	
Hemodynamics pre-procedure, mean ± SD			
Systolic blood pressure	128±26	130±26	
Diastolic blood pressure	74±15	75±16	
Heart rate in beats/min	78±18	78±19	
Diseased vessels, N/total (%)			
0	13/533 (2.4)	10/534 (1.9)	
1	166/533 (31.1)	157/534 (29.4)	
2	175/533 (32.8)	174/534 (32.6)	
3	178/533 (33.4)	193/534 (36.1)	
Infarct related vessel, N/total (%)			
Left anterior descending artery	221/515 (42.9)	223/517 (43.1)	
Left circumflex artery	93/515 (18.1)	79/517 (15.3)	
Right coronary artery	189/515 (36.7)	204/517 (39.5)	
Other	12/515 (2.3)	11/517 (2.1)	
Initial TIMI flow, N/total (%)			
0/1	288/526 (54.7)	316/531 (59.5)	
2	102/526 (19.4)	85/531 (16.0)	
3	136/526 (25.9)	130/531 (24.5)	

(Continued)

Table 1. Continued

	Thrombus aspiration (N=535)	Conventional PCI (N=536)	P-value
Procedural characteristics			
Final TIMI flow 3, N/total (%)	431/501 (86.0)	409/496 (82.5)	0.12
Distal epicardial vessel obstruction after PCI	25/446 (5.6)		
Peak creatine kinase in total, Median (IQR)	N=421, 565 (247 - 1506)	N=418, 637 (291 - 1420)	0.24
Time to creatine kinase in total hr, Median (IQR)	8 (5 - 12)	7 (5 - 12)	0.84
Peak creatine kinase-MB, Median (IQR)	N=406, 58 (24 - 118)	N=405, 63 (30 - 114)	0.46
Time to peak creatine kinase-MB in hr, Median (IQR)	7 (5 - 10)	7 (5 - 10)	0.80

CABG=coronary artery bypass grafting. PCI=percutaneous coronary TIMI=thrombolysis in myocardial infarction flow grade. IQR=Interquartile range.

METHODS

The study design, methods, and first results of the TAPAS trial have been reported previously.[2,9] TAPAS investigated whether thrombus aspiration was better than conventional treatment of angioplasty without thrombus aspiration during primary PCI in patients with myocardial infarction. The trial was a single-centre, randomised open study with blinded assessment of endpoints.

Patients

1071 consecutive patients were enrolled at the University Medical Centre Groningen between January, 2005, and December, 2006. Inclusion criteria were symptoms suggesting acute myocardial ischaemia of more than 30 min, time from symptom onset of less than 12 h, and ST-segment elevation of more than 0·1 mV in two or more leads on the ECG. Exclusion criteria were rescue PCI after thrombolysis and known existence of a concomitant disease with life expectancy less than 6 months. The institutional review board approved the study and all patients included in the trial provided written informed consent.

Treatment

Before initial coronary angiography, patients were randomly assigned in a 1:1 ratio to either thrombus aspiration or conventional treatment. In patients randomly assigned to thrombus aspiration, the Export Aspiration Catheter (Medtronic Corporation, California, USA) was used to establish antegrade flow before stenting. When necessary for stent delivery, balloon dila tion was done before stenting. In patients who received conventional treatment, balloon angioplasty was followed by stent placement (figure 1). All patients were pretreated with aspirin (500 mg followed by 80–100 mg per day), heparin (5000 IU),

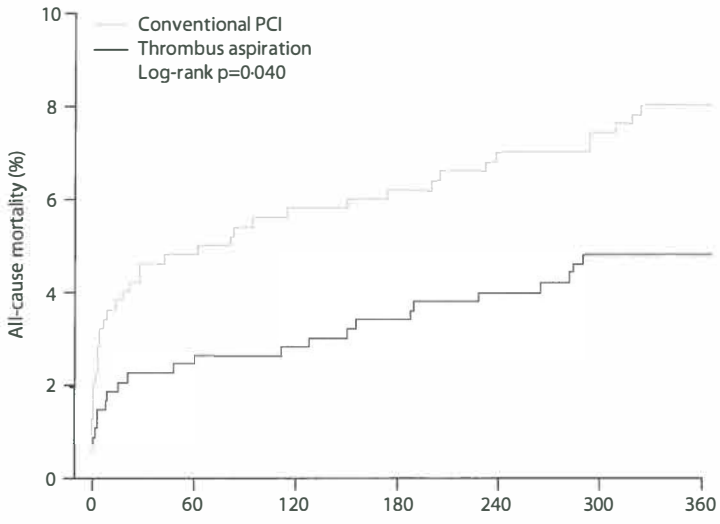
and clopidogrel (loading dose of 600 mg followed by 75 mg per day), which was admin istrated directly after electrocardiographic confirmation of ST-elevation myocardial infarction. Unless contra indicated, patients received weight-adjusted glycoprotein IIb/IIIa-inhibitor (abciximab) during the procedure and additional heparin guided by activated clotting time. Standard therapies after PCI included β blockers, lipid-lowering agents, and angiotensin-converting-enzyme inhibitors or angiotensin-II receptor antagonists, according to current guidelines.[10]

Table 2. Medication at a median of 438 (402–486) days follow-up

	Thrombus aspiration	Conventional PCI	P-value
Questionnaires send in total, N	199	193	
Information on medication, N/total (%)	149/199 (74.9)	140/193 (72.5)	
Duration of follow-up in days, median (IQR)	443 (400 - 493)	431 (402 - 486)	0.54
No medication, N/total (%)	1/149 (0.1)	0/140 (0.0)	0.94
Aspirin, N/total (%)	126/149 (84.6)	117/140 (83.6)	0.82
Clopidogrel, N/total (%)	13/149 (8.7)	21/140 (15.0)	0.10
Coumarine derivates, N/total (%)	28/149 (18.8)	25/140 (17.9)	0.84
Statins, N/total (%)	134/149 (89.9)	128/140 (91.4)	0.66
Beta-blocker	130/149 (87.9)	120/140 (85.7)	0.70
Metropolol	96/130 (73.8)	83/119 (69.7)	
Carvedilol	4/130 (3.1)	5/119 (4.2)	
Bisoprolol	25/130 (19.2)	28/119 (23.5)	
Sotalol	1/130 (0.8)	1/119 (0.8)	
Nebivolol	4/130 (3.1)	2/119 (1.7)	
Calcium channel blockers, N/total (%)	23/149 (15.4)	21/140 (15.0)	0.92
Nitrates, N/total (%)	11/149 (7.4)	10/140 (7.1)	0.94
Angiotensin-converting-enzyme inhibitor, N/total (%)	77/149 (51.7)	80/140 (57.1)	0.35
Angiotensin-II receptor antagonists, N/total (%)	30/149 (20.1)	29/140 (20.7)	0.90
Diuretics, N/total (%)	37/149 (24.8)	32/140 (22.9)	0.90

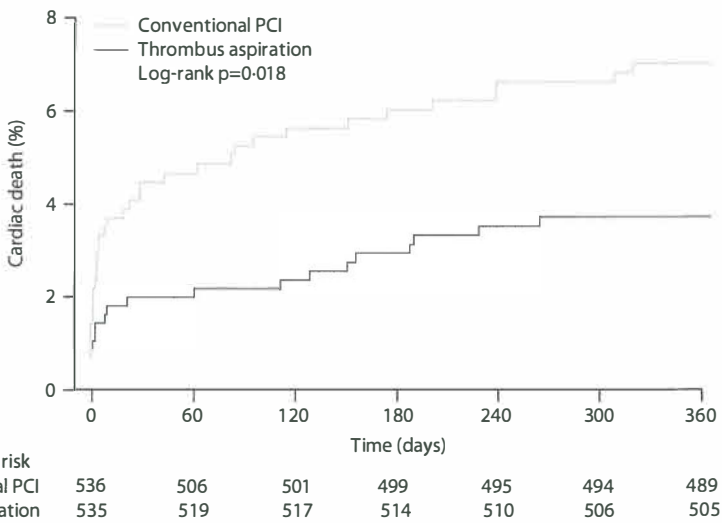
Outcome measures and follow-up

The primary efficacy endpoint of TAPAS was post-procedural frequency of myocardial blush grade 0 or 1. Secondary endpoints included post-procedural Thrombolysis in Myocardial Infarction (TIMI)-flow 3, complete ST-segment elevation resolution, no persistent ST-segment deviation, and 30-day and 1-year major adverse cardiac events.[9] Death was regarded as cardiac unless an unequivocal non-cardiac cause of death was established. Reinfarction was defined as recurrent symptoms with new ST-segment elevation and elevation of cardiac markers to at least twice the upper limit of normal. Angiographically proven stent thrombosis was defined as a complete or partial occlusion within the stented segment, with evidence of thrombus and reduced antegrade flow



Number at risk							
Conventional PCI	536	506	501	499	495	494	489
Thrombus aspiration	535	519	517	514	510	506	505
Total	1071	1025	1018	1013	1005	1000	994

Figure 2. Kaplan-Meier curve for all-cause mortality at 1-year follow-up



Number at risk							
Conventional PCI	536	506	501	499	495	494	489
Thrombus aspiration	535	519	517	514	510	506	505
Total	1071	1025	1018	1013	1005	1000	994

Figure 3. Kaplan-Meier curve for cardiac death at 1-year follow-up

(TIMI flow <3) with a concurrent acute clinical ischaemic event.[11] Distal embolisation after PCI was defined as a filling defect with abrupt cutoff in the vessel located distally of the culprit lesion.

Information on vital status, reinfarction, and coronary revascularisation procedures were assessed using hospital records, written questionnaires, and telephone interviews at or beyond 1 year after randomisation. Written questionnaires were also used to obtain information on medical therapy during follow-up. Vital status was also obtained from a central population registry. All major adverse cardiac events were assessed and classified by an interventional cardiologist who was unaware of the treatment allocation.

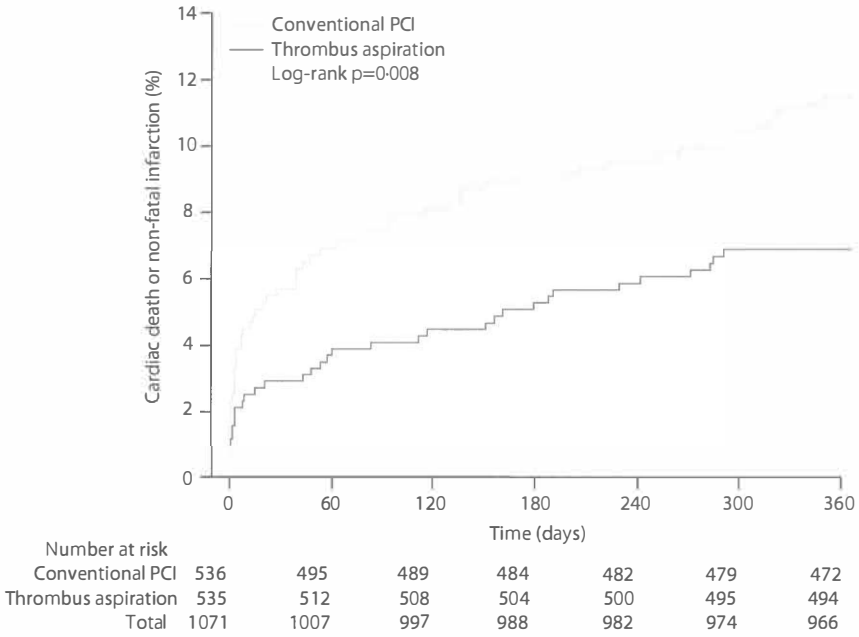


Figure 4. Kaplan-Meier curve for the combined endpoint of cardiac death or non-fatal reinfarction at 1-year follow-up.

Statistical analysis

Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous variables were compared using a two-tailed Student's t-test or Mann Whitney *U* test. Follow-up analysis was done using time-to-event data (for which patients were censored at the time of last follow-up). Hazard ratios and 95% CIs were estimated with a Cox's proportional hazard model, with treatment

as the only covariate. 1-year clinical outcomes were displayed using Kaplan Meier methodology and were compared with log-rank test pooled over strata. The relation between reperfusion parameters (myocardial blush grade and ST-segment elevation resolution) and clinical outcome were calculated using χ^2 tests. Univariate and multivariate

logistic-regression analyses were used for identifying risk factors for the combined endpoint of cardiac death or non-fatal reinfarction at 1 year follow-up. Baseline variables of the TIMI risk score[12] and treatment assignment were tested for their predictive value. These variables were age, diabetes, hypertension, systolic blood pressure at admission, heart rate at admission, weight, anterior myocardial infarction, total ischaemic time, and randomisation to thrombus aspiration. Significant variables at univariate analysis ($p<0.075$) were included in the multivariate model. Analyses were done according to the intention-to-treat principle. All p values were 2-tailed. Analyses were done with SPSS software version 14.0.2 (SPSS, Chicago, USA).

Table 3. Adverse clinical events at 1-year follow-up

	Thrombus aspiration N=535	Conventional PCI N=536	Hazard Ratio (95% CI)	P-value
All-cause mortality, N (%)	25 (4.7)	41 (7.6)	1.67 (1.02 - 2.75)	0.042
Cardiac death	19 (3.6)	36 (6.7)	1.93 (1.11 - 3.37)	0.020
Reinfarction	12 (2.2)	23 (4.3)	1.97 (0.98 - 3.96)	0.05
Target vessel revascularization	60 (12.9)	69 (11.2)	1.19 (0.84 - 1.68)	0.34
Second PCI target-vessel	37 (6.9)	51 (9.5)		
CABG target-vessel	25 (4.7)	20 (3.7)		
Cardiac death or Non-fatal reinfarction	30 (5.6)	53 (9.9)	1.81 (1.16 - 2.84)	0.009
Major Adverse Cardiac Events	89 (16.6)	109 (20.3)	1.26 (0.95 - 1.67)	0.10
Angiographically proven stent-thrombosis	6 (1.1)	12 (2.2)	2.05 (0.77 - 5.47)	0.15
Acute (24 hrs)	1 (0.2)	1 (0.2)		
Subacute (>1-30 days)	1 (0.2)	3 (0.6)		
Late (>30-365 days)	4 (0.7)	8 (1.5)		

CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention.

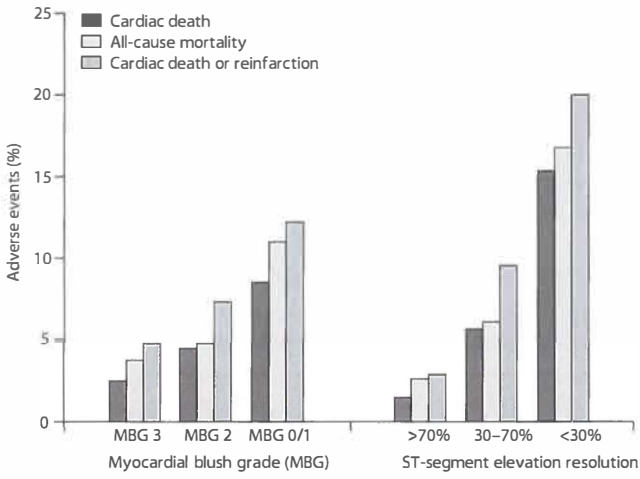
Role of funding source

The study was supported by an unrestricted grant from Medtronic (for angiographic analyses by the corelaboratory). All other costs were covered by the Thorax Centre of the University Medical Centre Groningen. Medtronic had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Vital status 1 year after randomisation was available for 530 (99.1%) patients in the thrombus aspiration group and for 530 (98.9%) in the conventional PCI group (figure 1). 54 patients (10%) in the thrombus aspiration group were crossed over to the conventional group because of a tortuous or distal infarct-related segment, and six patients (1%) in the

conventional group were crossed over to thrombus aspiration because of angiographic evidence of thrombus. Baseline clinical and angiographic characteristics were well balanced between the treatment groups (table 1).
Written questionnaires to obtain information on vital status, hospital admissions, and current medical therapy were sent to 392 patients at 1 year or more after randomisation. In 289 (73.7%) cases the questionnaire was sent back with information on current medical therapy (table 2).



Rate of cardiac death (%)	2·4	4·4	8·5	p=0·003	1·4	5·6	15·3	p<0·0001
Rate of all-cause mortality (%)	3·7	4·7	11·0	p=0·001	2·6	6·0	16·8	p<0·0001
Rate of cardiac death or reinfarction (%)	4·7	7·3	12·2	p=0·004	2·8	9·5	20·0	p<0·0001

Figure 5. Relation between parameters for myocardial reperfusion and total mortality, cardiac death, and the combined endpoint of cardiac death or non-fatal reinfarction at 1-year follow-up

66 patients died during 1-year follow-up. The number of deaths of cardiac origin was 55 (83.3%), of whom 30 died during the first 30 days and 25 between 30 days and 1 year. Of the 25 cardiac deaths after 30 days, ten occurred in the thrombus aspiration group and 15 in the conventional PCI group. Kaplan-Meier estimates for cardiac death after 30 days were 1.95% for thrombus aspiration and 3.00% for conventional PCI (log-rank p=0.284).
Causes of definite non-cardiac deaths were malignancy (n=8, including pulmonary cancer [3], hepatobiliary cancer [2], non-Hodgkin lymphoma [1], acute leukaemia [1], and prostate cancer [1]), septicaemia (n=1), trauma (n=1), and myelodysplastic syndrome (n=1). The Kaplan-Meier curves revealed a significant diff erence for 1-year all-cause mortality (log-rank p=0.040), cardiac death (log-rank p=0.018), and the combined endpoint of cardiac death or non-fatal reinfarction (log-rank p=0.008; figures 2, 3, and 4). The hazard ratios of adverse clinical events at 1-year follow-up are shown in table 3.
The primary endpoint of TAPAS was myocardial blush grade 0 or 1. Myocardial blush grade was associated with all-cause mortality (p=0.001), cardiac death (p=0.003), and the combined endpoint of cardiac death or non-fatal reinfarction (p=0.004) at 1-year follow-up. Moreover, the occurrence of clinical events at 1 year was also significantly related to ST-

segment elevation resolution (p<0.0001 for all associations; figure 5). Also, after exclusion of patients who died during the first 30 days, there was still a significant difference in distribution of cardiac death after 30 days according to myocardial blush grade: 4.4% (9 of 204) in myocardial blush grade 0 or 1, 1.6% (6 of 375) in grade 2, and 1.3% (5 of 377) in grade 3 (p=0.032).

Treatment assignment and variables of the TIMI-risk score were tested for their univariate and multivariate predictive value (table 4). Significant multivariate risk factors for cardiac death or nonfatal reinfarction were: assignment to thrombus aspiration (odds ratio 0.54; 95% CI 0.33–0.93; p=0.025); age (1.04; 1.02–1.06; p=0.001); diabetes (3.22; 1.80–5.74; p<0.0001); and heart rate at admission (1.02; 1.00–1.03; p=0.027).

Table 4. TIMI risk score variables of the combined endpoint of cardiac death or non-fatal reinfarction

	Univariate analysis			Multivariate analysis*		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Thrombus-aspiration	0.54	0.34 - 0.86	0.010	0.54	0.33 - 0.93	0.025
Age in yr	1.05	1.03 - 1.07	<0.0001	1.04	1.02 - 1.06	0.001
Diabetes	3.62	2.15 - 6.07	<0.0001	3.22	1.80 - 5.74	<0.0001
Weight in kg	0.98	0.96 - 0.99	0.010	0.98	0.96 - 1.00	0.07
Anterior myocardial infarction	1.69	1.07 - 2.67	0.026	1.61	0.97 - 2.66	0.06
Heart rate at admission	1.01	1.00 - 1.03	0.021	1.02	1.00 - 1.03	0.027
Systolic blood pressure at admission	1.00	0.99 - 1.01	0.50	-	-	-
Hypertension	1.18	0.74 - 1.87	0.49	-	-	-
Total ischemic time in hr	1.04	0.97 - 1.11	0.32	-	-	-

* Multivariate analysis of significant univariate risk factors p<0.075.

DISCUSSION

The main finding of this study is that a strategy of thrombus aspiration before stenting during primary PCI results in a lower cardiac mortality and a lower incidence of the combined endpoint of cardiac death or non-fatal reinfarction than does normal therapy alone.

Previous studies have reported that visually assessed myocardial blush is an important parameter for myocardial reperfusion after primary PCI and is strongly associated with infarct size, recovery of ventricular function, and mortality.[1,13] Additionally, resolution of ST-segment elevation has proven to be an independent predictor of long-term mortality.[14] In line with these previous studies, we noted a strong association between these parameters for myocardial reperfusion and clinical events at both 30 days and 1 year in TAPAS. Also, after exclusion of patients who died during the first 30 days, there was still a significant association between cardiac death and myocardial blush grade. The benefit in improved parameters for myocardial reperfusion seen in the thrombus aspiration group resulted in less clinical events at 30 days.[2] Our study shows that this beneficial effect on reperfusion

translates into a significant improvement of clinical outcome at 1 year.

The effect of manual thrombus aspiration on parameters for myocardial reperfusion has been widely investigated. However, randomised data for clinical outcome are scarce. Two small randomised trials have been published investigating the effect of thrombus aspiration on left ventricular remodelling. The myocardial contrast echocardiography substudy of the REMEDIA Trial5 enrolled 50 patients randomly assigned to thrombus aspiration or standard PCI. Thrombus aspiration was associated with a significant reduction in severity and extent of myocardial obstruction at 24 h, which was sustained at 1 week and 6 months. Additionally, end-diastolic and end-systolic left ventricular volumes were slightly, but not significantly, smaller in patients undergoing thrombus aspiration. De Luca and colleagues[6] showed that, in 76 patients with anterior myocardial infarction, thrombus aspiration was associated with significantly lower end-diastolic and end-systolic left ventricular volumes at 6 months than with conventional PCI. Although these trials show promising results, sample sizes were small and accuracy of echocardiography in assessing left ventricular function is relatively moderate compared with contrast-enhanced MRI.

In TAPAS, the mortality benefit and the reduced reinfarction rates in the thrombus aspiration group were probably associated with less thrombotic complications associated with the treatment. Less distal embolisation will result in improved myocardial perfusion[2–4] and left ventricular function,[5,6] and in a survival benefit at follow-up.[15] Thrombus aspiration reduced the source of distal embolisation by removing the clots as well as atherosclerotic plaque material exposed to the luminal surface after plaque rupture. Histopathological analysis of aspirated clots in TAPAS showed both so-called white clots, composed mainly of platelets, and red clots composed of fibrin and red blood cells.[2] Thrombus aspiration is therefore of additional value during primary PCI, since currently used antiplatelet agents mainly target white platelet clots. Furthermore, in TAPAS there were less reinfarctions in the thrombus aspiration group, contributing to the survival benefit. This lower reinfarction rate seems to be at least in part caused by a reduction in thrombotic complications, such as stent thrombosis, after thrombus aspiration. The presence of thrombus, in particular a large thrombus-load, has been associated with incomplete stent apposition,[16] reinfarction,[17] and stent-thrombosis at follow-up.[11] Therefore, a reduction in thrombus-load by thrombus aspiration could be expected to result in less reinfarction at follow-up.

Other elements contributing to the favourable outcome of manual thrombus aspiration are its simplicity (indicated by similar duration of fluoroscopy and door-to-balloon times as the control group) and safety (no flow-limiting dissections or other device-related complications occurred during the procedure).[2] 1-year target vessel revascularisation did not show an eff ect of thrombus aspiration on clinical recurrence. Therefore, our results do not indicate an eff ect of thrombus aspiration on neointima hyperplasia compared with conventional PCI.

TAPAS was designed to detect diff erences in myocardial reperfusion and—with 1071 patients, 66 deaths, and 35 reinfarctions—had limited power to investigate the magnitude of the eff ect of thrombus aspiration on clinical outcome. Another limitation of our study was that no systematic measurement of infarct size and left ventricular function was done. These data could have offered additional information on the mechanism behind the clinical benefit seen in the thrombus aspiration group.

In conclusion, compared with conventional PCI, thrombus aspiration before stenting of the infarct-related artery results in improved myocardial perfusion and seems to improve clinical outcome 1 year after PCI for ST-elevation myocardial infarction.

Acknowledgments

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CHAPTER 7

Predictors of effective thrombus aspiration in patients with ST-elevation myocardial infarction

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ABSTRACT

Objective

To investigate which patient characteristics are independent predictors of thrombus retrieval and whether manual thrombus aspiration should be recommended for use in all patients or in a more selected population with ST-elevation myocardial infarction (STEMI).

Background

Manual thrombus aspiration devices are increasingly used during primary percutaneous coronary intervention (PCI) for STEMI. This in an attempt to reduce the incidence and amount of PCI-induced distal embolisation by removing atherothrombotic material exposed to the lumen.

Methods

We performed an analysis on all patients with STEMI treated with routine manual thrombus aspiration between January 2005 and May 2010 in our center. Thrombus aspiration was defined as effective when atherothrombotic material was seen in the aspirate.

Results

A total of 1712 patients underwent thrombus aspiration, which was effective in 82.6%. Multivariate independent predictors of effective thrombus aspiration were reference vessel diameter >3mm, angiographic visible thrombus and total ischemic time >3hours. However, the discriminative value of these predictors together was low, with an area under the ROC-curve of 0.60 (CI 0.56–0.64, $p<0.0001$). The institutional and individual learning curves showed that improvement of efficacy occurred with increasing volume, indicating that thrombus aspiration may also be operator related.

Conclusion

This analysis demonstrates that routine manual thrombus aspiration in STEMI patients is feasible and results in successful thrombus retrieval in the majority of the patients. The high efficacy rates across all patient subgroups support a strategy of routine thrombus aspiration over a more selective approach.

INTRODUCTION

Thrombus aspiration devices are increasingly used in the setting of primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI). This in an attempt to reduce the incidence and amount of PCI-induced distal embolisation by removing atherothrombotic material exposed to the lumen.[1,2] Besides that thrombus load can be a source of distal embolisation, it also has been associated with the occurrence of other adverse events such as stent undersizing, malapposition and stent thrombosis.[3-5] Recent randomized controlled trials[6-11] and meta-analyses[12,13] demonstrated that manual thrombus aspiration results in improved myocardial reperfusion and clinical outcome.
The efficacy rate of thrombus aspiration (as defined as retrieval of atherothrombotic material) ranges between 73 and 95 percent in published randomized controlled trials.[9,10] However, current trials investigated thrombus aspiration in a routine setting and not in selected patients groups. In addition, study sizes were often too small to perform adequate subgroup analyses.[6-11] It is therefore currently unclear which patient characteristics are independent predictors of effective thrombus aspiration and whether thrombus aspiration should be recommended for use in all patients or in a more selected population.
In the present analysis, we investigated the feasibility and efficacy of routine thrombus aspiration in an all-comers population treated between 2005 and 2010 in our center. Analyses were performed to identify independent predictors of effective thrombus aspiration, which were subsequently tested for their discriminative and clinical value. In addition, institutional and individual learning curves for thrombus aspiration were analysed.

METHODS

In the University Medical Center Groningen all patients undergoing primary PCI for STEMI were included in a prospective registry. In the year 2005 and 2006 thrombus aspiration was performed in the setting of the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS).[8,9] After the trial was finished, thrombus aspiration became the preferred strategy for patients with STEMI in our center.

Patients

All patients treated with primary PCI for STEMI between January 2005 and May 2010 in our center were enrolled in the present analysis. Inclusion criteria were: onset of symptoms <12 hours or in case of persisting symptoms due to ongoing ischemia <24 hours, ST-segment elevation >0.1mV in 2 or more leads on the electrocardiogram and a culprit lesion suitable for PCI. We compared patients characteristics of those in which thrombus aspiration was attempted with those who did not undergo thrombus aspiration. Patients in who thrombus aspiration as initial intervention was attempted were used in analyses to identify independent predictors of effective thrombus aspiration. Patients randomized to conventional PCI in the TAPAS trial were excluded. No other exclusion criteria were used.

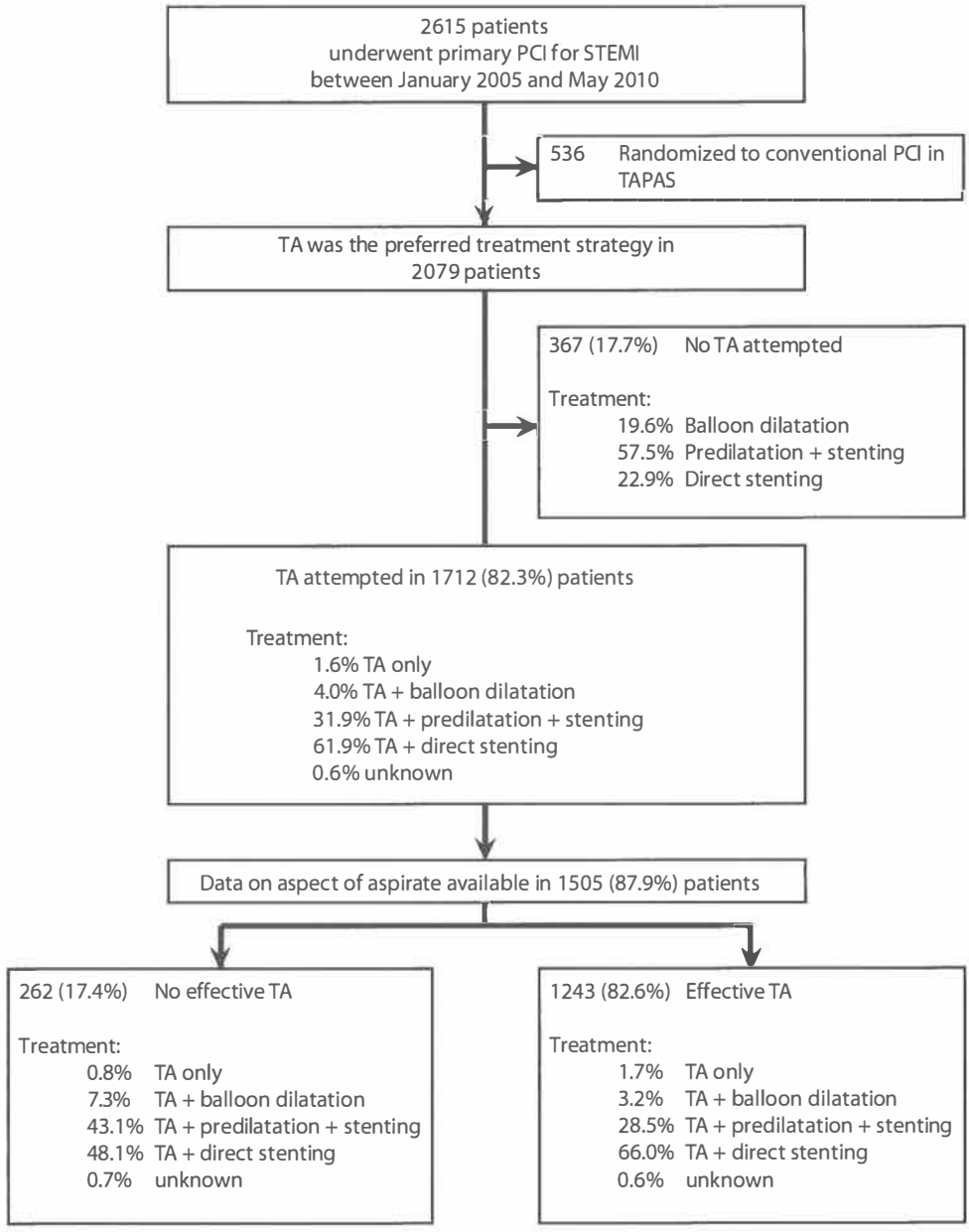

Figure 1. Flowdiagram. PCI= Percutaneous coronary intervention, STEMI= ST-elevation myocardial infarction, TA= Thrombus aspiration, TAPAS= Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study.

Treatment

All patients were pre-treated with aspirin, heparin and clopidogrel, which was administered directly after electrocardiographic confirmation of STEMI. Patients received weight-adjusted glycoprotein IIb/IIIa-inhibitor (Abciximab) during the procedure and additional activated clotting time-guided heparin, unless contraindicated. The Export Aspiration Catheter (Medtronic Corporation, California, USA) was used in the majority of the patients to establish antegrade flow before stenting. From January 2007 to March 2007 the Diver Clot Extraction (Invatec, Roncadelle, Italy) was also used.[14] When necessary for stent delivery, balloon dilatation was performed before stenting.

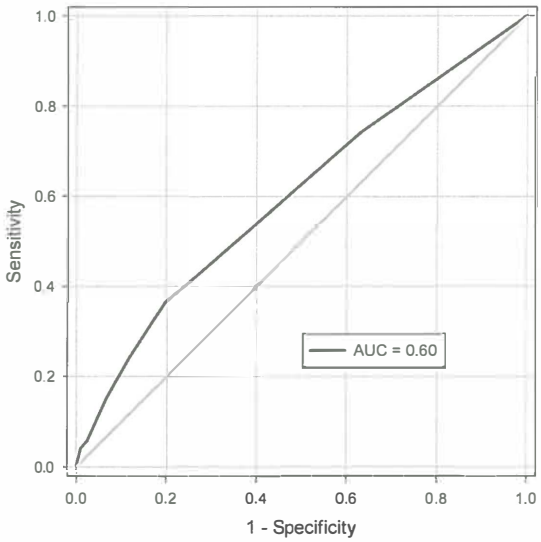

Figure 2. ROC curve for effective thrombus aspiration

Definitions and endpoints

Attempted thrombus aspiration included all cases in which thrombus aspiration was performed as initial strategy to establish coronary flow. Aspiration was defined as effective when atherothrombotic material was seen in the aspirate by the treating interventional cardiologist or by histopathological examination in a selection of the patients. For histopathological examination, aspirated material during thrombus aspiration was placed in formalin, and fixed for 24 hours. Histological sections were cut and stained with hematoxylin-eosin for examination with a light microscope (x100) performed by independent pathologists.[8] All coronary angiographic data were analysed by an independent core laboratory (Cordinamo, Wezep, the Netherlands) or 2 experienced observers blinded to all clinical data. Thrombolysis In Myocardial Infarction (TIMI) flow grade and angiographic visible thrombus were scored as previously described.[15,16]

Table 1. Baseline, angiographic and procedural characteristics

	Thrombus aspiration attempted			Effective thrombus aspiration		
	No	Yes	P-value	No	Yes	P-value
Patients, N/total (%)	367/2079 (17.7)	1712/2079 (82.3)		262/1505 (17.4)	1243/1505 (82.6)	
Age in yr, mean±SD	67.8 ± 12.7	63.3 ± 12.9	<0.0001	64.2 ± 12.9	62.6 ± 12.7	NS
Male sex, N/total (%)	256/367 (69.8)	1235/1712 (72.1)	NS	183/262 (69.8)	919/1243 (73.9)	NS
Risk factors						
Diabetes	57/326 (17.5)	178/1685 (10.6)	<0.0001	37/260 (14.2)	122/1228 (9.9)	0.042
Hypertension	132/296 (44.6)	624/1644 (38.0)	0.031	108/254 (42.5)	444/1205 (36.8)	NS
Previous CABG	15/366 (4.1)	38/1704 (2.2)	0.040	7/260 (2.7)	24/1238 (1.9)	NS
Previous MI	64/341 (18.8)	150/1689 (8.9)	<0.0001	23/258 (8.9)	111/1232 (9.0)	NS
Previous PCI	45/366 (12.3)	120/1706 (7.0)	0.001	14/261 (5.4)	90/1239 (7.3)	NS
Three vessel disease	134/367 (36.5)	474/1710 (27.7)	0.001	82/261 (31.4)	331/1242 (26.7)	NS
Systolic BP ≤90 mmHg at admission	43/246 (17.5)	129/1611 (8.0)	<0.0001	15/249 (6.0)	92/1208 (7.6)	NS
Total ischemic time						
Median (IQR)	211 (145 - 350)	185 (130 - 286)	<0.0001	195 (139 - 320)	180 (127 - 279)	0.028
>3 hrs	177/286 (61.9)	842/1591 (52.9)	0.005	147/249 (59.0)	608/1193 (51.0)	0.020
>6 hrs	70/286 (24.5)	280/1591 (17.6)	0.006	48/249 (19.3)	196/1193 (16.4)	NS
Location culprit lesion			<0.0001			NS
LAD	140/367 (38.1)	733/1712 (42.8)		120/262 (45.8)	533/1243 (42.9)	
LCx	68/367 (18.5)	265/1712 (15.5)		47/262 (17.9)	183/1243 (14.7)	
RCA	128/367 (34.9)	687/1712 (40.1)		91/262 (34.7)	512/1243 (41.2)	
Left main artery	23/367 (6.3)	14/1712 (0.8)		1/262 (0.4)	9/1243 (0.7)	
Graft	8/367 (2.2)	13/1712 (0.8)		3/262 (1.1)	6/1243 (0.5)	
AHA/ACC lesion characteristic C	186/363 (51.2)	682/1672 (40.8)	<0.0001	103/262 (39.3)	504/1243 (40.5)	NS
Proximal location	151/367 (41.1)	701/1712 (40.9)	NS	103/262 (39.3)	562/1243 (45.2)	NS
Thrombus visible pre	305/357 (85.4)	1478/1709 (86.5)	NS	202/262 (77.1)	1091/1243 (87.8)	<0.0001
TIMI flow 0/1 pre	219/362 (60.5)	1073/1708 (62.8)	NS	140/261 (53.6)	794/1240 (64.0)	0.002
Reference vessel diameter >3mm	235/308 (76.3)	1044/1242 (84.1)	0.001	199/257 (77.4)	1036/1229 (84.3)	0.008
Number of stents implanted	1.3 ± 1.0	1.3 ± 0.7	NS	1.3 ± 0.7	1.3 ± 0.7	NS
Mean stent diameter	3.3 ± 0.5	3.3 ± 0.5	0.029	3.3 ± 0.5	3.4 ± 0.4	0.003
Mean stent length	19.6 ± 6.7	19.9 ± 6.5	NS	20.5 ± 6.6	19.8 ± 6.5	NS
Glycoprotein IIb/IIIa inhibitor	250/367 (68.1)	1571/1712 (91.8)	<0.0001	238/262 (90.8)	1161/1243 (93.4)	NS
Intra aortic balloon pump	73/355 (20.6)	124/1687 (7.4)	<0.0001	10/261 (3.8)	80/1224 (6.5)	NS

BP = blood pressure, CABG = coronary artery bypass grafting, LAD = left anterior descending artery, LCx = left circumflex artery, MI = myocardial infarction, RCA = Right coronary artery, TIMI flow = thrombolysis in myocardial infarction flow grade.

Statistics

Data are presented as frequency (percentage), mean ± standard deviation or as median (interquartile range). Categorical variables were compared with the use of the chi-square test or Fisher's exact test. Continuous variables were compared with the use of two-tailed Student's t-test or Mann Whitney U-test. Univariate and multivariate logistic regression analyses were used to detect independent predictors of effective thrombus aspiration and retrieval of thrombi >1mm. The following eighteen variables were tested for their predictive value: gender (male), diabetes, current smoking, hypertension, hypercholesterolemia, body mass index >30, previous myocardial infarction, previous PCI, previous CABG, culprit vessel location, systolic blood pressure ≤90mmHg at admission, age, total ischemic time, angiographic visible thrombus pre, TIMI flow pre, reference vessel diameter, AHA/ACC lesion type, three vessel disease. Significant univariate predictors ($p<0.15$) were tested for their multivariate predictive value. To investigate the discriminative value of the multivariate predictors, receiver operating characteristic (ROC) curves were drawn using predictive probabilities of each patient. Goodness-of-fit of the multivariate models were tested using the Hosmer-Lemeshow chi-square test. In addition, analyses of institutional and individual learning curves were performed. The institutional learning curve was investigated between January 2005 and July 2009, as in this period the same six interventional cardiologists performed all procedures in our center. To correct for differences in patient population, the categorical variable "Time" (subgroups of 1 year, with 2009 as reference year) was adjusted for significant multivariate predictors of effective thrombus aspiration. Individual learning curves were analysed of the six operators which performed all procedures between January 2005 and July 2009, and were calculated by dividing the patients of each operator into subgroups of 15 consecutive patients. All p-values were 2-tailed, with statistical significance set at <0.05. Analyses were performed using SPSS software version 16.0.2 (SPSS, Chicago, Illinois).

RESULTS

A total of 2615 patients underwent primary PCI for STEMI between January 2005 and May 2010 (see figure 1). Of these patients, 536 (20.5%) were randomized to conventional PCI in the context of the TAPAS trial and therefore excluded from this analysis.

Thrombus aspiration attempted

Thrombus aspiration was attempted in 1712/2079 (82.3%) patients (Table 1 and Figure 1). The group in which thrombus aspiration was not attempted was older (67.8 vs. 63.3yr), had longer total ischemic times (median 211 vs. 185 min) and more often three vessel disease (36.5 vs. 27.7%) and left main disease (6.3 vs. 0.8%). Although initial TIMI flow rate and incidence of visible thrombus before PCI were similar in both groups, patients in which thrombus aspiration was not attempted had a higher rate of additional balloon dilatation and lower rate of direct stenting (figure 1).

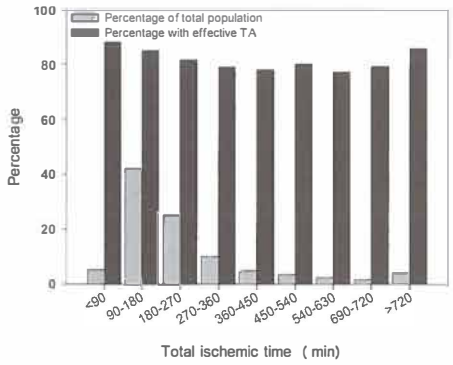

Figure 3A. Ischemic time and effective thrombus aspiration

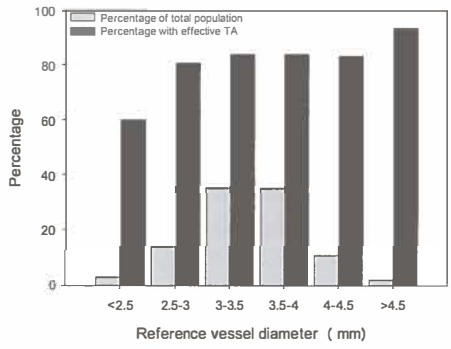

Figure 3B. Vessel diameter and effective thrombus aspiration

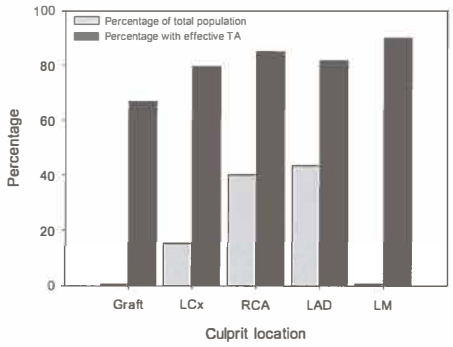

Figure 3C. Culprit location and effective thrombus aspiration

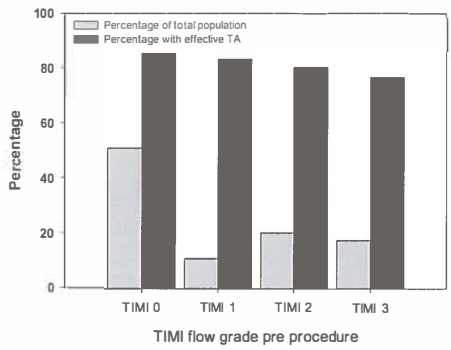

Figure 3D. TIMI flow grade and effective thrombus aspiration

Effective thrombus aspiration

In 1712 patients thrombus aspiration was attempted as initial strategy to establish coronary flow. In 1505/1712 (87.9) patients data was available on efficacy. Thrombus aspiration was effective in 1243/1505 (82.6) patients (table 1). In these patients atherothrombotic material was retrieved, confirmed by either histopathological analysis and/or the operator. As compared with those without effective thrombus aspiration, these patients had less often diabetes, shorter total ischemic times, more often angiographic visible thrombus and larger reference vessel diameters. No significant differences were found regarding baseline variables such as age, sex and other cardiovascular risk factors.

Nine variables were significant at univariate analyses and were tested for their predictive multivariate value (see table 2). Total ischemic time >3 hours, a reference diameter of >3mm and angiographic visible thrombus were significant predictors in the multivariate model. However, the area under the ROC curve of this multivariate model was only 0.60 (CI 0.56 – 0.64, p<0.0001) (figure 2). The poor discriminative value of univariate and

multivariate predictors of effective thrombus aspiration is supported by figures 3A-D, which illustrate high efficacy rates across all subgroups.

Institutional and individual learning curves

Between January 2005 and July 2009 all interventions were performed by the same six interventional cardiologists. During these years, the efficacy rate of thrombus aspiration increased from 66% in 2005 to 95% in 2009 (figure 4A). The relation between time (years after introduction) and efficacy rate remained significant after adjusting for multivariate predictors of effective thrombus aspiration (p<0.0001). Also the individual learning curves of the six operators during the first 105 aspiration procedures demonstrated that higher efficacy rates were achieved with increasing number of patients treated with thrombus aspiration (figure 4B).

Table 2. Predictors of effective thrombus aspiration

	Univariate predictors, p<0.15			Multivariate predictors, p<0.05		
	OR	95% CI	p	OR	95% CI	p
Age >65yrs	0.78	0.60 - 1.02	0.07	0.88	0.66 - 1.18	0.40
Hypertension	0.79	0.60 - 1.04	0.09	0.81	0.60 - 1.09	0.16
Diabetes	0.67	0.45 - 0.99	0.043	0.77	0.50 - 1.21	0.26
Total ischemic time >3 hrs	0.72	0.55 - 0.95	0.021	0.73	0.54 - 0.98	0.033
Three vessel disease	0.79	0.59 - 1.06	0.12	0.84	0.62 - 1.16	0.29
Culprit location - RCA	1.32	1.00 - 1.74	0.05	1.21	0.89 - 1.64	0.23
Reference vessel diameter >3mm	1.57	1.12 - 2.18	0.008	1.45	1.02 - 2.08	0.041
TIMI flow pre 0/1	1.54	1.18 - 2.02	0.002	1.28	0.91 - 1.81	0.16
Angiographic visible thrombus	2.17	1.56 - 3.03	<0.0001	1.87	1.22 - 2.86	0.004

CI = Confidence interval, OR = Odds Ratio, RCA = Right coronary artery, TIMI flow = thrombolysis in myocardial infarction flow grade.

Histopathological analyses

Histopathological analyses were performed in 490/1505 (32.6) of patients who underwent thrombus aspiration. Histopathological analyses demonstrated thrombi larger than 1mm in 128/490 (26.1) of patients. Regression analyses identified the following multivariate independent predictors for retrieval of thrombi larger than 1mm: angiographic visible thrombus (OR 2.92, CI 1.22 – 6.99, p=0.016), reference diameter of >3mm (OR 2.23, CI 1.04 – 4.76, p=0.039), three vessel disease (OR 0.38, CI 0.22 – 0.67, p=0.001), age >65jrs (OR 0.51, CI 0.31 – 0.84, p=0.009), diabetes (OR 0.34, CI 0.12 – 0.94, p=0.037) and hypercholesterolemia (OR 0.52, CI 0.29 – 0.94, p=0.031)). The discriminate value of this multivariate model was low, given an area under the ROC of 0.72 (CI 0.67 – 0.77, p<0.0001)

DISCUSSION

This analysis demonstrated that thrombus aspiration in STEMI patients is feasible and effective in the majority of the patients. Independent predictors for effective thrombus aspiration were vessel diameter, presence of angiographic visible thrombus and total ischemic time. Nevertheless, high efficacy rates were achieved across all patient subgroups, which support a strategy of routine thrombus aspiration in STEMI patients undergoing primary PCI over a more selective approach.

Recent randomized studies demonstrated that manual thrombus aspiration results in improved myocardial reperfusion as compared with conventional PCI.[6-11] These findings have driven the use of thrombus aspiration devices in routine clinical practice. However, the discussion about which subgroups will benefit more from thrombus aspiration and which less is still ongoing.[17,18] As a result patients undergoing thrombus aspiration are often selected on baseline or angiographic characteristics, both in daily clinical practice as in setting of prospective studies. However, evidence supporting the exclusion of specific patient subgroups is lacking. This study offers more insight on which patient characteristics influence efficacy rates of thrombus aspiration and to which extend.

In the present analyses routine thrombus aspiration resulted in a high efficacy rate of 82.6% in an all-comers STEMI population. Also when we define cases in which the operator decided not to attempt thrombus aspiration as not effective thrombus aspiration, the efficacy rate is still very acceptable (68%). This rate is comparable with most previous studies, such as the TAPAS trial (73%),[8] EMERALD trial (73%),[11] and the study of Kramer et al (74%) [19]. These high efficacy rates are likely to be related to the good, all-round applicability of current manual thrombus aspiration catheters. In addition, although in some patients no angiographic visible thrombus was present, aspiration may still be successful and effective due to the presence of mural thrombus.[19-21]

We found that the efficacy rate of thrombus aspiration is mainly influenced by coronary anatomy characteristics (vessel diameter) and presence of thrombus on the initial angiogram. Furthermore, total ischemic time longer than 3 hours was associated with a lower efficacy rate. This is most likely explained by more organised thrombi, which are less friable and more difficult to aspirate.[19] Further, the institutional and individual learning curves showed that improvement of efficacy occurred with increasing volume, indicating that effective thrombus aspiration may also be operator related.[22,23] This operator dependence of thrombus aspiration could be related to increased experience in performing the procedure or better selection of patients who would benefit from thrombus aspiration. Further, it could also be explained by an increased focus of operators on retrieval of atherothrombotic material after the positive results of the TAPAS trial in 2007. Nevertheless, the TAPAS trial performed between 2005 and 2006, demonstrated that thrombus aspiration can be safely performed during this possible learning curve, as during this period no complications were observed related with thrombus aspiration.[9]

Reduction of thrombus load is likely to reduce the incidence and amount of distal embolisation and improve myocardial reperfusion. However, in the present study no analyses were performed on myocardial reperfusion or outcome, as thrombus aspiration was performed in a routine fashion without a large conventional PCI control group. In the TAPAS study, subanalyses did not demonstrate significant differences in clinical benefit

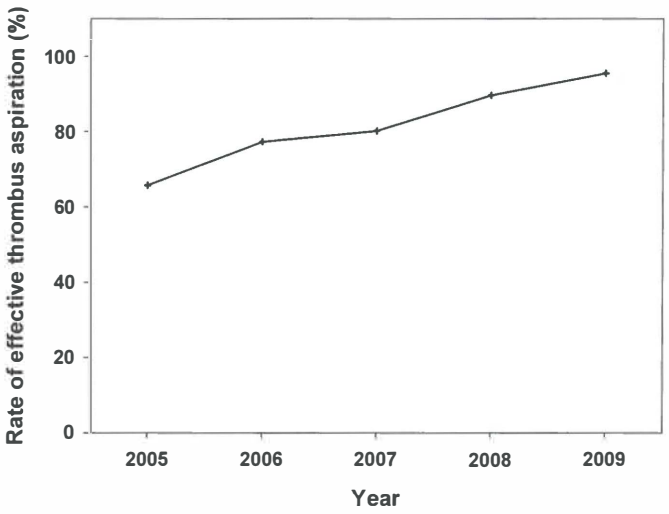

Figure 4A. Institutional learning curve

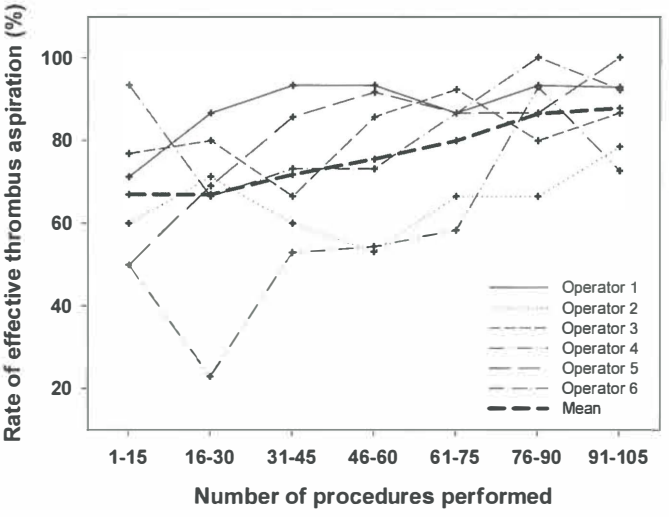

Figure 4B. Individual learning curves

of thrombus aspiration across prespecified subgroups (TIMI flow, age, sex, total ischemic time, infarct related vessel, proximal lesion and thrombus seen on initial angiogram).[9] Also in a recent meta-analysis of individual patient data of most thrombus aspiration trials (n=2686), no differences were found across these subgroups or other baseline patient characteristics.[12] Further, although several independent predictors for effective thrombus aspiration were found in the present analyses, the discriminative value of these predictors

together were low. In addition, efficacy rates remained high in all patient subgroups. These results support the routine application of thrombus aspiration in all patients undergoing primary PCI for STEMI.
This large single-center retrospective study on predictors of effective thrombus aspiration suffers from several limitations. Only a part of aspirated material underwent histopathological analyses and the majority was scored by the interventional cardiologist. Further, although thrombus aspiration was performed routinely in our center, and no exclusion criteria were used, it was not attempted in all patients. In some high risk subgroups thrombus aspiration was less often performed; for example, in patients with an IABP or a culprit lesion in a graft. This may indicate that some selection by the operators may have been performed, however, also in these high risk patients thrombus aspiration was still attempted in the majority of the cases (IABP 63% and culprit in graft 62%).

In conclusion, this analysis demonstrates that routine thrombus aspiration in STEMI patients is feasible and effective in the majority of the patients. The high efficacy rates across all patient subgroups support a strategy of routine thrombus aspiration in STEMI patients undergoing primary PCI over a more selective approach.

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CHAPTER 8

A Comparison of 2 Thrombus Aspiration Devices With Histopathological Analysis of Retrieved Material in Patients Presenting With ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Objectives

The objective of this study was to compare 2 manual thrombus aspiration catheters inunselected patients with ST-segment elevation myocardial infarction.

Background

Distal embolization is common during percutaneous coronary intervention in STsegment elevation myocardial infarction and can induce impaired myocardial perfusion. Several aspiration thrombectomy devices have been introduced to prevent distal embolization, however, withconflicting clinical results. Currently, it is unclear to what extent this variance in outcome can be explained by device-related factors, such as internal lumen size.

Methods

We performed a prospective cohort study in which patients undergoing primary percutaneous coronary intervention were treated with a large-internal-lumen catheter (Diver, Invatec, Roncadelle, Italy). Outcomes were compared with a matched population of the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) trial, in which patients were treated with a medium-sized catheter (Export, Medtronic, Minneapolis, Minnesota). A histopathological analysis was performed of retrieved material.

Results

A total of 160 patients, treated with the Diver (n = 80) or Export (n = 80) aspiration catheter, were enrolled. Effective thrombus aspiration was seen in 70.3% of the patients treated with the Diver catheter versus 81.8% with the Export catheter (p = 0.10) No significant difference was found in myocardial blush grade or electrocardiographic outcome between the 2 devices. Size distribution of retrieved thrombotic particles was similar per device. Erythrocyte-rich thrombi were found in 34.8% of the cases and were predominately seen in patients with low initial Thrombolysis In Myocardial Infarction flow grade (p = 0.008).

Conclusions

A larger internal lumen diameter does not result in retrieval of larger thrombotic particles, nor in improved angiographic or electrocardiographic outcomes.

INTRODUCTION

Distal embolization is common during percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) and can induce impaired myocardial perfusion.[1,2] Several aspiration and thrombectomy devices have been introduced to prevent distal embolization. These include the Diver (Invatec, Roncadelle, Italy), Export (Medtronic, Minneapolis, Minnesota), Probing (Boston Scientific, Natick, Massachusetts), Pronto (Vascular Solutions, Minneapolis, Minnesota), and Rescue catheters (Boston Scientific, Natick, Massachusetts).[3-8] The ideal aspiration catheter should be rapidly exchangeable, good deliverable (also in small diameter and tortuous culprit vessels), and at the same time have sufficient lumen size to aspirate thrombus material. Based on internal lumen diameter, aspiration catheters can be subdivided into 3 size groups: large (Diver, 0.062 inch; Pronto, 0.065 inch), medium (Export, 0.041 inch; Rescue, 0.042 inch), and small (Probing, 0.018 inch). Currently, it is unknown whether large-lumen-diameter catheters are able to aspirate larger thrombotic components when compared with smaller sized ones. Retrieval of larger particles could improve the efficacy of thrombus aspiration, leading to better myocardial perfusion after primary PCI. On the other hand, a larger lumen diameter could influence handling characteristics and device safety.

To test the hypothesis that a large-lumen-diameter catheter is capable of aspirating larger thrombotic components, we performed a prospective cohort study in which patients undergoing primary PCI were treated with a large-diameter catheter (Diver catheter). Further, because histopathological analysis of aspirated debris has only been performed in small and selected study populations,[8-10] we also performed a histopathological assessment of retrieved material.

Histopathological, angiographic, and clinical outcomes were compared with a matched population of the TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study), in which patients were treated with a medium-sized catheter (Export catheter).[3]

MATERIALS AND METHODS

Enrollment in the TAPAS trial ended December 2006.[3] From January 2007 to March 2007, all patients who underwent PCI in a native vessel for STEMI were included in this prospective study. Inclusion and exclusion criteria were similar to that for the TAPAS trial. In summary, patients were considered eligible for inclusion when they had symptoms suggesting acute myocardial ischemia >30 min, time from symptom onset was <12 h, and ST segment elevation >0.1 mV in ≥2 contiguous leads was present on the electrocardiogram (ECG). Patients were excluded when they underwent rescue PCI after thrombolysis, had known existence of a disease with life expectancy <6 months, or no informed consent was given. Consecutive patients treated with the Diver catheter were matched with patients included in the TAPAS study, in which thrombus aspiration with the Export catheter was attempted.[3] Matching was based on the following variables: gender, initial Thrombolysis In Myocardial Infarction (TIMI) flow grade ±1, age ±5 years, and segment culprit lesion.

The primary end point is incidence of aspirated thrombotic components >1 mm. Secondary

end points are myocardial blush grade, ST-segment elevation resolution, persistent ST-segment elevation, enzymatic infarct size, postprocedural distal embolization, and major adverse cardiac events at 30 days.
The angiographic, histopathological, and electrocardiographic methods used in this study were similar to those used in the TAPAS trial.[3]

Description of the thrombusaspiration catheters

The PCI was performed using standard percutaneous techniques. The Export aspiration catheter (Medtronic) and the Diver Clot Extraction (Invatec) are both 6-F compatible thrombus aspiration catheters. The Export has an oblique aspiration tip design, with an aspiration lumen of 0.041 inch. The Diver has a distal aspiration lumen of 0.062. In both aspiration catheters, suction is provided by hand with a lockable 20-ml syringe. All interventional cardiologists were experienced in the usage of manual thrombus aspiration catheters. In addition, because the usage of both aspiration catheters is similar, no learning curve was expected in the Diver group.

Medication

Before PCI, the patient was treated with aspirin (a bolus of 500 mg), intravenous heparin (5000 IU), and clopidogrel (a loading dose of 600 mg). Adjunctive therapy included nitroglycerin intravenously and glycoprotein IIb/IIIa inhibitors. During PCI, additional heparin is administered guided by activated clotting time measurements. Standard therapies after PCI included aspirin 80 mg, clopidogrel 75 mg, beta-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Angiographic, electrocardiographic, and clinical outcome

Intravenous nitroglycerin was given after the procedure and before the final angiogram in all patients. The TIMI flow grades will be estimated as previously described: grade 0: no perfusion, grade 1: penetration without perfusion, grade 2: partial perfusion, grade 3: complete perfusion.[11] The evaluation of myocardial blush grades will be performed as described by van't Hof et al.[1]: grade 0: no myocardial blush, grade 1: minimal myocardial blush or contrast density, grade 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery, and grade 3, normal myocardial blush or contrast density comparable with that obtained during angiography of a contralateral or ipsilateral non–infarctrelatedcoronary artery. Persisting myocardial blush (staining) suggests leakage of contrast medium into the extravascular space and is graded 0. Distal embolization was considered to have occurred if new circumscribed filling defects and/or abrupt cut-off of the vessel distal to the target lesion appears. Thrombus was assessed according to the criteria summarized by Mabin et al.[12] The coronary angiograms were analyzed offline by 2 experienced observers.
A 12-lead ECG was acquired at presentation and after the PCI procedure. The post-procedural ECG was analyzed by comparison to the ST-segments of the ECG at presentation. ST-segment elevation resolution was categorized as complete (≥70%),

partial (30% to 70%), or absent (<30%). Persistent ST-segment deviation, defined as the sum of ST-segment depression and ST-segment elevation, was categorized into <2 mm, 2 to 10 mm, and ≥10 mm.
Clinical status (death, reinfarction, and ischemia-driven target vessel revascularization) was collected from hospitalrecords as well as by telephone interviews at 30 dayspost-procedure.

Histopathological analysis

Filtered material obtained during aspiration was analyzed using the same method as used in the TAPAS trial. In short, material was placed in formalin and fixed for 24 h. Thereafter, filtered material was pelleted by centrifugation in liquid agar 65°C in an Eppendorf tube. After the agar pellet was solidified at 4°C, it was embedded in paraffin using an automated tissue processor. Paraffin sections were cut at 4 µm and stained with hematoxylin-eosin for microscopical examination (×100). Immunostaining was performed to optimize visualization of endothelial cells, smooth muscle cells, and macrophage foam cells. Samples were classified into effective or no effective aspiration based on the presence of thrombotic material. Identified material was classified into 4 types: thrombus with only platelets, thrombus with an erythrocyte component, thrombus with atheromatous plaque, and thrombus with both erythrocyte and atheromatous plaque and in 5 size groups: residue (very small filter casts of loosely cohesive platelets), well-formed thrombi smaller than 0.5 mm, 0.5 to 1 mm, 1 to 2 mm, and >2 mm.

Statistical methods

The primary end point of this study is the incidence of aspirated thrombotic components >1 mm. Based on earlier experience with the Export catheter,[3] it was estimated that we needed to enroll 160 patients to achieve a power of 80% (with a 2-sided significance level of 0.05) to detect a increase from 35% to 55% with the Diver catheter.
Values are shown as means ± standard deviations, median (inner quartile range [IQR]), or numbers of patients (percentages). Differences in baseline characteristics and outcomes were tested using either paired sample t test or Wilcoxon signed-rank test. Nonpaired, univariate, and multivariate logistic regression analysis were used to assess independent predictors associated with effective thrombus aspiration and histological subsets. Significant variables at univariate analysis ($p < 0.15$) were included in multivariate models. The following variables were evaluated: gender, catheter, age, ischemic time, hyperlipidemia, diabetes, current smoking, pre-angina pectoris, body mass index, 3-vessel disease, TIMI flow grade beforehand, thrombus visible beforehand, and severe calcification.
All p values were 2-tailed, with statistical significance set at 0.05. Analyses were performed using SPSS software version 12.0.1 (SPSS Inc., Chicago, Illinois).

Table 1. Baseline and procedural characteristics

	Diver (n = 80)	Export (n = 80)	p-value
Age, years (mean ± SD)	62.4 ± 12.0	62.5 ± 11.5	0.94
Male gender	61/80 (76.3)	61/80 (76.3)	1.00
Body mass index (median, IQR)	26.1 (24.2 -29.4)	26.2 (24.2 - 29.3)	0.79
Risk factors			
Diabetes	6/79 (7.6)	15/79 (19.0)	0.019
Hypertension	25/78 (32.1)	26/75 (34.7)	0.85
Hyperlipidemia	24/71 (33.8)	18/67 (26.9)	0.57
Current smokers	40/79 (50.6)	40/73 (54.8)	0.87
Family history	43/78 (55.1)	44/79 (55.7)	1.00
Previous CABG	1/80 (1.3)	1/79 (1.3)	1.00
Previous Myocardial infarction	7/80 (8.8)	9/79 (11.4)	0.60
Previous PCI	3/80 (3.8)	7/79 (8.9)	0.16
Pre-infarct angina	42/77 (54.5)	30/77 (39.0)	0.07
Symptom duration, hr (median, IQR)	3.3 (2.0 - 5.3)	3.2 (2.2 - 5.6)	0.82
Hemodynamics pre-procedure			
Systolic blood pressure (mean ± SD)	123.5 ± 25.6	129.7 ± 28.1	0.12
Diastolic blood pressure (mean ± SD)	74.7 ± 14.8	75.1 ± 15.4	0.95
Pulse pressure (mean ± SD)	81.6 ± 23.9	76.6 ± 18.8	0.13
Three vessel disease	24/78 (30.8)	26/77 (33.8)	0.71
Peri-procedural GP IIb/IIIa inhibitors	71/80 (88.8)	77/80 (96.3)	0.08
Treated vessel			
LAD	31/80 (38.8)	31/80 (38.8)	1.00
RCA	34/80 (42.5)	34/80 (42.5)	-
Severely calcified lesion	14/80 (17.5)	12/80 (15.0)	0.90
Birfucation lesion	31/80 (38.8)	24/80 (30.0)	0.47
TIMI flow pre procedure			
0/1	57/80 (71.3)	54/80 (67.5)	0.49
2	13/80 (16.3)	16/80 (20.0)	-
3	10/80 (12.5)	10/80 (12.5)	-
Thrombus visible pre	43/80 (53.8)	40/75 (53.3)	0.87
TIMI flow 3 post PCI	70/80 (87.5)	67/80 (83.8)	0.52
Stent diameter, mm, (mean ± SD)	3.3 ± 0.4	3.4 ± 0.5	0.22
Stent length, mm, (mean ± SD)	19.9 ± 6.6	21.3 ± 7.3	0.34
Peak CK-MB (median, IQR)	72.8 (28.1 - 130.0)	68.0 (27.6 - 123.0)	0.19
Time to peak CK-MB, hr (median, IQR)	6.6 (4.3 - 9.9)	6.8 (5.1 - 8.8)	0.90
Peak CK-total (median, IQR)	686.2 (244.4 - 1283.4)	764.1 (291.6 - 1451.8)	0.99
Time to peak CK-total, hr (median, IQR)	7.2 (4.2 - 10.9)	7.1 (5.1 - 9.9)	0.72

CABG = Coronary Artery Bypass Grafting, CK = Creatine kinase, IQR = Interquartile range, PCI = Percutaneous Coronary Intervention, SD = standard deviation, TIMI = Thrombolysis In Myocardial Infarction flow grade.

RESULTS

A total of 82 consecutive patients were included. Two very young patients had no matching control patient within 5 years and were therefore excluded from the analysis. Baseline characteristics of the 80 enrolled patients are shown in Table 1.

Angiographic and electrocardiographic outcome

No serious complications, such as flow-limiting dissections or air embolization, occurred in the Diver or the Export group. A stent was placed in 91.3% (73 of 80) of the Diver patients and in 93.8% (75 of 80) of the Export patients. Direct stenting (stenting after thrombus aspiration without balloon pre-dilatation) was performed in 42.5% (31 of 73) of the patients treated with the Diver catheter and in 53.3% (40 of 75) treated with the Export (p = 0.39). Distal embolization post PCI was seen in 6.3% (5 of 80) of the patients in the Diver group and in 5.8% (4 of 70) in the Export group (p = 0.74). TIMI flow grade post-procedure and myocardial blush grade were similar in both groups (Table 1, Fig. 1).

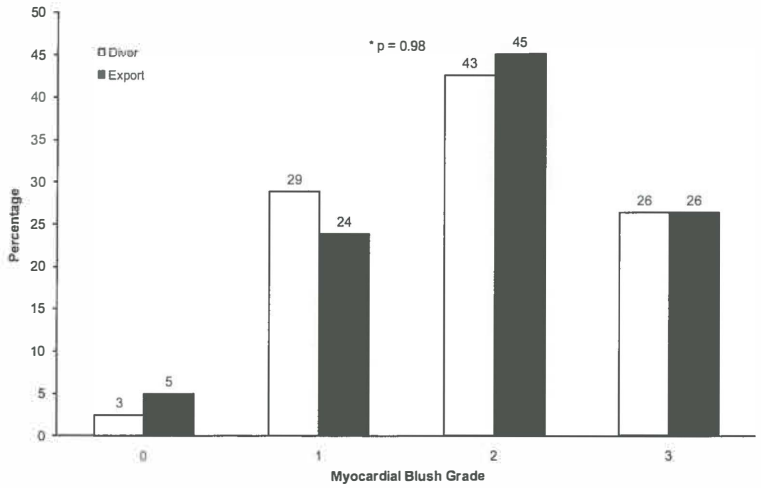

Figure 1. Myocardial blush grade after percutaneous coronary intervention

The ECGs for persistent ST-segment deviation analysis were available in 92.5% (148 of 160) of the patients and for ST-segment elevation resolution analysis in 91.3% (146 of 160). Median (IQR) time between balloon angioplasty and post-PCI ECG was 0.7 (0.5 to 0.9) h in the Diver group and 0.7 (0.6 to 1.1) h in the Export group (p = 0.37). Persistent ST-segment deviation <2 mm and >70% STsegment elevation resolution was seen in the majority of the patients treated with thrombus aspiration, respectively 52.0% (77 of 148) and 64.4% (94 of 146). No differences were seen in rates of persistent ST-segment deviation <2 mm, 2 to 10 mm and >10 mm between the Diver (49.3%, 39.7%, and 11.0%) and Export group (54.7%, 33.3%, and 12.0%) (p = 0.38) (Fig. 2). Incidences of ST-segment elevation resolution <30%, 30% to 70% and >70% were also similar in patients treated with the Diver (15.5%, 16,9%, and 67.6%) and the Export patients (14.7%, 24.0%, and 61.3%) (p = 0.97) (Fig. 3).

Short-term clinical outcome

Follow-up was completed in 100% of the patients. Occurrence of death, reinfarction, and target vessel revascularization within 30 days were similar in both groups. One death occurred in the Export group (0% vs 1.3%, p = 0.32). In the Diver group 2 reinfarctions occurred, compared with 1 in the Export group (2.5% vs 1.3%, p = 0.57). Five patients underwent target vessel revascularizations in the Diver group, compared with 4 in the Export group (6.3% vs 5.0%, p = 0.74). The incidence of the combined end point of death, reinfarction, or target vessel revascularization was 7.5% (6 of 80) in the Diver group versus 6.3% (5 of 80) in the Export group (p = 0.76).

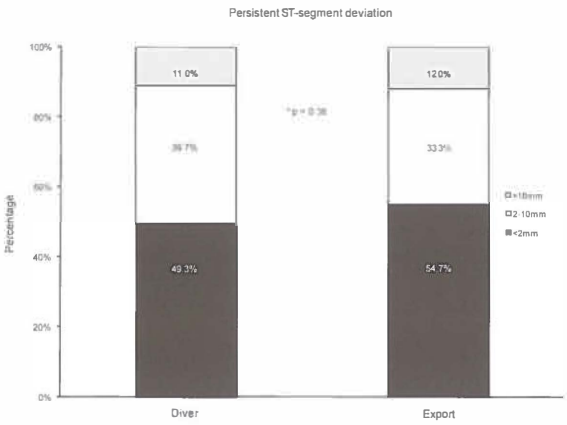

Figure 2. Persistent ST-segment deviation

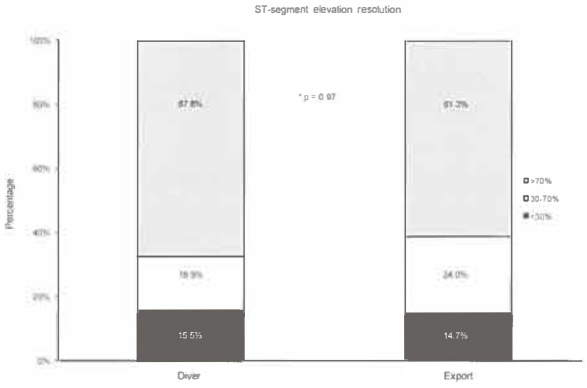

Figure 3. ST-segment elevation resolution

Histopathological assessment

Effective thrombus aspiration was seen in 70.3% (52 of 74) of the patients treated with the Diver catheter versus 81.8% (63 of 77) of the Export patients (p = 0.10). Aspirated thrombotic components >1 mm were found in 44.4% (28 of 63) of the Export patients and in 34.6% (18 of 52) of the Diver patients (p = 0.51). The size distribution of retrieved thrombotic particles was also similar for the 2 devices (p = 0.61) (Fig. 4).
Erythrocyte-rich thrombi and thrombi with plaque components were found in respectively

26.9% (14 of 52) and 7.7% (4 of 52) of the patients treated with the Diver and in 22.2% (14 of 63) and 14.3% (9 of 63) of the patients treated with the Export catheter. Thrombi with both plaque and erythrocytes components were seen in 13.5% (7 of 52) of the Diver patients and in 7.9% (5 of 63) of the Export patients. Distribution of histological subsets was similar in the 2 groups (p = 0.47).

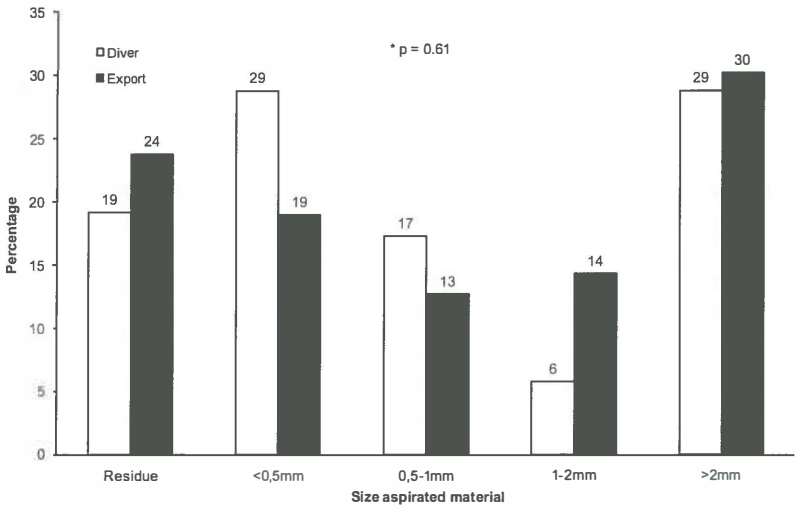

Figure 4. Size distribution of aspirated material

The relationship between histopathological findings and baseline characteristics was investigated using logistic regression (Table 2). Thrombus was visible on the initial angiogram in the majority of the patients; however, this was not associated with retrieval of material at univariate logistic regression (p = 0.70). Multivariate analysis showed that thrombus aspiration with the Export catheter was not an independent predictor of effective thrombus aspiration (p = 0.09). Independent predictors for erythrocyte-rich thrombi at multivariate analysis were low initial TIMI flow grade (p = 0.008) and absence of 3-vessel disease (p = 0.026).

DISCUSSION

This prospective cohort study shows that the Export and Diver catheters are both safe and effective in removing thrombus in an unselected population with ST-segment elevation myocardial infarction. The larger internal lumen diameter of the Diver catheter did not result in retrieval of larger thrombotic particles, nor in improved angiographic or electrocardiographic outcomes.

Primary PCI does not always result in successful reperfusion of the myocardium, despite a patent epicardial vessel. Mechanical crushing and fragmentation of the thrombuscontaining lesion during primary PCI is thought to be at least partly responsible for myocardial dysfunction after PCI.[13–15] Several devices have been introduced to facilitate removal of thrombus and plaque material, thereby protecting the microvasculature

and improving myocardial blood flow. In saphenous vein graft PCI, distal embolic protection devices have proven to be very effective in preventing distal embolization (class I recommendation, level of evidence A).[16] In primary PCI for native coronary lesions, aspiration thrombectomy devices may be most useful because their size allows access to the lesion over a routine wire. The DEAR-MI (Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction) trial randomized 155 patients to thrombus aspiration with the Pronto catheter or to primary PCI alone.[5] Thrombus aspiration in this trial was associated with significantly better ST-segment resolution, better myocardial blush grade, and less distal embolization compared with primary PCI. The results of the TAPAS trial (Export aspiration catheter) and the REMEDIA (Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolization by Thrombus-Aspiration in Primary and Rescue Angioplasty) trial (Diver aspiration catheter), which compared thrombus aspiration with primary PCI, reported also feasibility and applicability of this approach.[3,6] Conflicting results came from the trial of Kaltoft et al.,[7] which enrolled 215 patients to thrombus aspiration with the Rescue catheter or primary PCI. This study reported larger final infarct size and a trend toward less myocardial salvage associated with thrombus aspiration. In the abovementioned studies, 4 different aspiration devices were used. It is unclear to what extent these conflicting results can be explained by device-related factors. One major difference between these devices is internal lumen diameter. An aspiration catheter with insufficient capacity to aspirate can theoretically manipulate and dislodge the thrombus, causing an adverse effect on myocardial perfusion. This present study shows that both medium-lumen and large-lumen thrombus aspiration catheters are safe and effective in terms of high rates of myocardial blush grades 2 to 3 and ST-segment normalization.

Table 2. Multivariate logistic regression analysis of significant baseline characteristics (p<0.15) on effective thrombus aspiration and erythrocyte-rich thrombi

Dependent variable	Co-variable	Exp (B) (95% CI)	P-value
Effective thrombus aspiration			
	Catheter (Export)	2.07 (0.90 to 4.76)	0.09
	Diabetes	0.39 (0.13 to 1.14)	0.08
	Hyperlipidemia	0.48 (0.21 to 1.11)	0.09
Erythrocyte-rich thrombi			
	Ischemic time (hrs)	1.07 (0.98 to 1.18)	0.15
	Three vessel disease	0.32 (0.12 to 0.87)	0.026
	TIMI flow pre	0.54 (0.34 to 0.85)	0.008

CI = confidence interval; Exp (B) = exponentiation of the B coefficient; TIMI = Thrombolysis In Myocardial Infarction flow grade, pre = pre angioplasty procedure.

The size distribution of retrieved particles did not differ significantly between the 2 catheters; however, especially in the range 1 to 2 mm, some difference could be detected in favor of the Export catheter. These differences can be caused by differences in distal tip design between the 2 catheters. The nonsuperiority of a larger-lumen catheter may be explained by the fact that freshly formed thrombi are easily friable. Whether a larger-lumen

catheter has a benefit in the context of older occlusions and degenerated saphenous vein grafts, in which particles are less friable, is currently unclear.

Previous angioscopic studies in patients with acute coronary syndromes suppose erythrocyte-rich thrombi to be present in the majority of the patients with acute myocardial infarction.[17,18] Our study found a lower incidence of erythrocyte-rich thrombi (34.8%, 40 of 115). Erythrocyterich thrombi were predominantly seen in patients with low initial epicardial flow in combination with a trend for longer ischemic time. This supports the thought that erythrocyterich thrombi are formed mainly during stasis of blood flow, whereas white thrombi are predominately seen in patients with TIMI flow grade 1 to 3 at presentation.[17–20] The lower incidence of erythrocyte-thrombi in our study can be explained by the fact that most previous observations date from the thrombolytic era, whereas nowadays patients are pretreated with heparin, aspirin, and clopidogrel during transportation to a PCI facility. These antithrombotic agents can induce enhancement of lysis and dissolvement of thrombus, causing pharmacological reperfusion before the initial angiogram.[21,22]

In our study we compared 2 manual thrombus-aspiration catheters. However, there are several types of adjunctive mechanical devices for reducing distal embolization. Recently a meta-analysis has been published combining the results of 21 randomized trials investigating the impact of adjunctive mechanical devices to prevent distal embolization.[4] In this analysis, the benefit in terms of better myocardial perfusion and less distal embolization was more apparent in studies investigating the impact of thrombectomy as compared with distal protection devices. Whether there is a difference in efficacy between different types of adjunctive mechanical devices (for example, mechanical thrombectomy vs manual thrombus aspiration) is currently unclear in the context of STEMI, because no direct comparisons have been performed.

This study has several limitations. Both study groups were followed up prospectively and matched for age, gender, initial TIMI flow grade, and infarct-related segment, but bias of unknown confounders still might exist. Our histopathological analysis provides information on aspiration capacity in terms of presence of thrombotic material and size of aspirated particles. However, no analysis was performed on the total volume of retrieved debris. A distal embolic protection device may be useful for investigating differences in the volume ratio of aspirated versus distal embolic debris, but these devices are only feasible in a selected group of patients.

CONCLUSION

The present study shows that manual aspiration catheters are safe and effective in removing thrombus in patients with ST-segment elevation myocardial infarction. A larger internal lumen diameter did not result in retrieval of larger thrombotic particles, nor in improved angiographic or electrocardiographic outcomes.

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CHAPTER 9

The feasibility and safety of routine thrombus aspiration in patients with non-ST-elevation myocardial infarction

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ABSTRACT

Objectives

To investigate the feasibility and safety of manual thrombus aspiration in patients undergoing percutaneous coronary intervention (PCI) for non-ST-elevation myocardial infarction (NSTEMI).

Background

Myocardial necrosis in patients with acute coronary syndromes may be a sign of microvascular obstruction, owing to spontaneous or PCI-induced embolization of atherothrombotic material. Manual thrombus aspiration results in improved myocardial reperfusion in patients undergoing PCI for ST-elevation myocardial infarction. Currently, no published data on thrombus aspiration in patients with NSTEMI are available.

Methods

As part of a prospective cohort study, 70 patients undergoing PCI for NSTEMI were treated with thrombus aspiration (Export Aspiration Catheter, Medtronic, Minneapolis, MN). Histopathological analysis was performed on aspirated material.

Results

Thrombus aspiration was effective in 58 patients (83%) and resulted in a marked reduction of TIMI-thrombus score 4/5 (40% pre- versus 7% postthrombus aspiration) and increase of the rate of TIMI-flow 3 (36% pre- versus 66% postthrombus aspiration). The incidence of myocardial blush grade 2 and 3 were 39 and 45%, respectively. Distal embolization was visible in three patients (4%) on the final angiogram.

Conclusion

This study demonstrates that thrombus aspiration in most NSTEMI patients is feasible and safe and is associated with a high rate of retrieval of thrombotic material.

INTRODUCTION

Acute coronary syndromes (ACS) are initiated by an eroded, fissured, or ruptured atherosclerotic plaque, leading to subsequent platelet aggregation and thrombus formation. Myocardial necrosis occurs when the resultant thrombus induces (transient) epicardial occlusion, but may also be a sign of microvascular obstruction, owing to spontaneous or percutaneous coronary intervention (PCI)-induced embolization of atherothrombotic material.[1-3] Recently, we have demonstrated that manual thrombus aspiration is effective in patients undergoing PCI for ST-elevation myocardial infarction (STEMI).[4,5] At the present time, no published data on thrombus aspiration in patients with non-ST-elevation myocardial infarction (NSTEMI) are available.

In this prospective cohort study, we have investigated the feasibility and safety of thrombus aspiration (Export Aspiration Catheter, Medtronic, Minneapolis, MN) in patients undergoing PCI for NSTEMI. In addition, a histopathological analysis was performed on aspirated material.

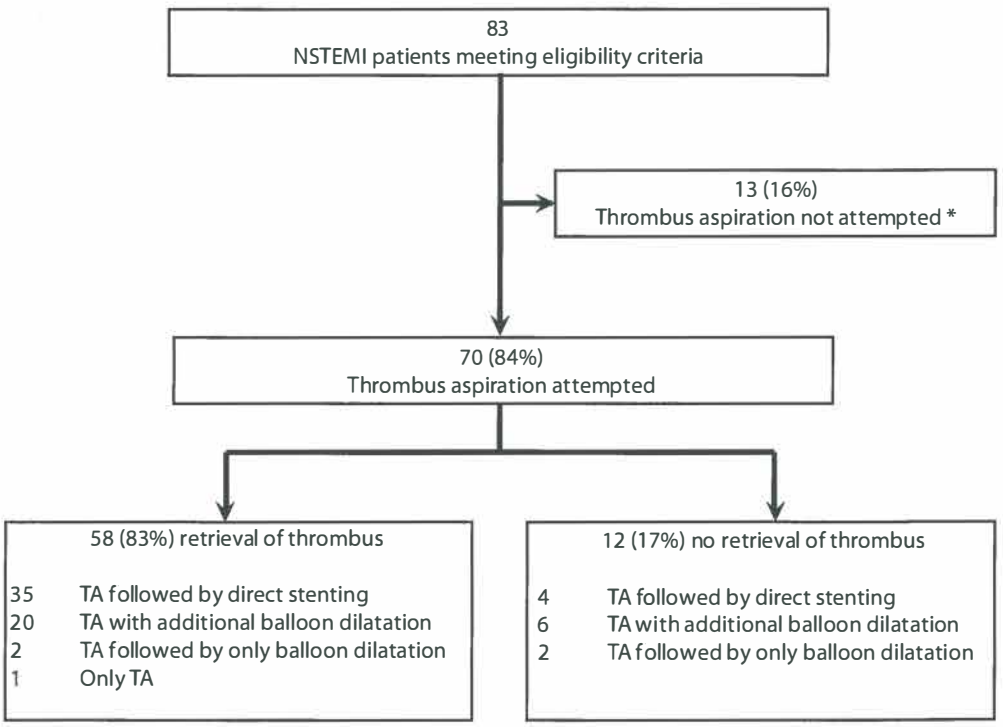

Figure 1. Study flow diagram
*** The operator decided that thrombus aspiration was not feasible because of left main stenosis (N=2) and small and/or tortuous vessel (N=11). NSTEMI = non-ST-elevation myocardial infarction, TA = Thrombus aspiration.**

MATERIALS AND METHODS

Patients who underwent PCI for NSTEMI were included in this prospective study. NSTEMI was defined as chest pain at rest, time from last chest pain to angiography less than 24 hr, an ECG with ST-segment shifts and/or T-wave changes, and a positive cardiac troponin T. No angiographic subsets of patients were excluded.

Device and Procedure Characteristics

The Export Aspiration Catheter (Medtronic, Minneapolis, MN) is a 6F compatible thrombus aspiration catheter with an aspiration lumen of 0.041 in. and a crossing profile of 0.068 in. Suction is performed by hand with lockable 20-ml syringes.

After crossing the ischemia-related lesion with a guide wire, the Export Aspiration Catheter was advanced into the target segment during continuous aspiration. The number of passages, necessary to achieve an optimal result, was left over to the judgment of the operator, but at least 2 × 20 ml was aspirated in multiple passages. Additional balloon angioplasty was performed when necessary for stent delivery. All interventional cardiologists were experienced in performing manual thrombus aspiration.[4]

Medication

Before PCI, the patient was treated with aspirin (a bolus of 500 mg), intravenous heparin (5,000 IU), and clopidogrel (a loading dose of 600 mg). Adjunctive therapy included nitroglycerin and glycoprotein (GP) IIb/IIIa inhibitors. During PCI, additional heparin was administered guided by ACT measurements. Standard therapies after PCI included aspirin 80 mg, clopidogrel 75 mg, beta-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Risk Stratification, Angiographic, and Clinical Outcome

The risk for in-hospital mortality was calculated using the GRACE-risk score[6] and divided in low (probability in-hospital death <1%), intermediate (1– 3%), and high (>3%). Coronary angiograms were analyzed off-line by an experienced interventional cardiologist. Intracoronary nitroglycerin was given after the procedure and before the final angiogram in all patients. Thrombolysis in myocardial infarction (TIMI) flow grades and myocardial blush grades (MBG) were estimated as previously described.[2] Distal embolization was defined as circumscribed filling defects and/or abrupt cut off of the vessel distal to the target lesion on the final angiogram after the PCI procedure. Thrombus was assessed according to the criteria summarized by Mabin et al.[7] and thrombus load was graded from 0 to 5 according to the TIMI-thrombusscore.[8]

Clinical status (death, reinfarction, and ischemia driven target vessel revascularization) was collected from hospital records as well as by telephone interviews at 30 days postprocedure.

Table 1. Baseline and procedural characteristics

	N = 70
Age, years (mean ± SD)	61.1 ± 11.9
Male gender	55/70 (78.6)
Body mass index (median, IQR)	26.2 (24.8 - 28.7)
Risk factors	
Diabetes	4/70 (5.7)
Hypertension	32/68 (47.1)
Hyperlipidemia	33/62 (53.2)
Current smokers	27/69 (39.1)
Family history	41/68 (60.3)
Previous CABG	4/70 (5.7)
Previous Myocardial infarction	7/70 (10.0)
Previous PCI	8/70 (11.4)
Hemodynamics pre-procedure	
Systolic blood pressure (mean ± SD)	126.8 ± 23.3
Diastolic blood pressure (mean ± SD)	75.6 ± 12.0
Heart rate, beats/min (mean ± SD)	76.3 ± 16.4
Peri-procedural GP IIb/IIIa inhibitors	55/70 (78.6)
Severely calcified lesion	14/70 (20.0)
Bifurcation lesion	30/70 (42.9)
TIMI flow pre procedure	
0/1	23/70 (32.9)
2	22/70 (31.4)
3	25/70 (35.7)
TIMI flow 3 post procedure	61/70 (87.1)
TIMI-thrombus-score pre thrombus aspiration	
0/1	33/70 (47.1)
2	3/70 (4.3)
3	6/70 (8.6)
4/5	28/70 (40.0)
TIMI-thrombus-score post thrombus aspiration	
0/1	52/67 (74.3)
2	6/67 (9.0)
3	4/67 (6.0)
4/5	5/67 (7.5)
Stent implanted	65/70 (92.9)
Stent diameter, mm, (mean ± SD)	3.3 ± 0.5
Stent length, mm, (mean ± SD)	18.6 ± 5.8
Peak Troponin T (median, IQR)	1.0 (0.2 - 2.7)
Time to peak Troponin T , hr (median, IQR)	4.8 (1.6 - 4.8)
Peak CK-total (median, IQR)	317.0 (104.5 - 1120.5)
Time to peak CK-total, hr (median, IQR)	4.4 (0.3 - 8.7)
Peak CK-MB (median, IQR)	52.5 (20.3 - 131.5)
Time to peak CK-MB, hr (median, IQR)	2.9 (0.3 - 9.9)

CABG = Coronary Artery Bypass Grafting, IQR = Interquartile range, PCI = Percutaneous Coronary Intervention, SD = standard deviation, TIMI = Thrombolysis In Myocardial Infarction flow grade.

Histopathological Analysis

Filtered material obtained during aspiration was analyzed using the same method as used in the TAPASstudy.[4,9] Effective thrombus aspiration was defined as the presence of atherothrombotic material in the aspirate samples. Identified material was classified based on the composition (white platelet thrombus vs. red erythrocyte-rich thrombus) and size of aspirated and filtered atherothrombotic material, as well as on the presence of plaque components. Material was divided in three size groups: small (very small filter casts of loosely cohesive platelets and thrombi smaller than 0.5 mm), medium (thrombi 0.5–2 mm), and large (thrombi >2 mm).

Statistical Analysis

Uni- and multivariate regression analyses were performed to identify predictors of effective thrombus aspiration and improved TIMI flow (difference between pre- and postthrombus aspiration TIMI flow). The following variables were tested: age (years), sex (male), total ischemic time (hr), hypertension, diabetes, hypercholesterolemia, current smoking, previous MI, heart rate at admission, systolic blood pressure, body mass index, anterior MI, periprocedural GPIIb/IIIa, number of vessels diseased, proximal infarctrelated segment, thrombus visible pre, stent diameter (as estimate of vessel diameter). Significant variables at univariate analysis ($P < 0.15$) were included in the multivariate model. All P-values were two-tailed, with statistical significance set at <0.05. Analyses were performed using SPSS software version 14.0.2 (SPSS, Chicago, IL).

RESULTS

Between January 2007 and August 2007, 83 patients met the eligibility criteria. In 13/83 patients (16%), the operator decided not to attempt thrombus aspiration because of left main stenosis (N = 2) and small and/or tortuous vessel (N = 11). In 70/83 patients (84%), thrombus aspiration was attempted. The characteristics and outcomes of these 70 patients are described in detail in this analysis (see Fig. 1).

Baseline Characteristics

The mean age was 61 ± 12 years (see Table I). The GRACE-risk scores for in-hospital mortality were low in 26%, intermediate in 32%, and high in 42% of the patients. The ischemia-related artery was the right coronary artery in 43%, left anterior descending artery in 29%, left circumflex artery in 23%, and a venegraft in 4%. Multivessel disease was present in 56% of the patients.

Angiographic and Clinical Outcomes

Thrombus was visible on the initial angiogram in 36 patients (51%). No complications such as flow limiting dissections or air embolization occurred during thrombus aspiration. Thrombus aspiration was associated with a marked reduction of TIMI-thrombus score 4/5 (40% pre- versus 7% postthrombus aspiration) and increase of the rate of TIMI-flow 3 (36% pre- versus 66% postthrombus aspiration). Direct stenting was performed in 39 patients

(55.7%) (see Fig. 1 and Table I). Incidence of post-PCI TIMI-flow 3 was 87%. The incidence of myocardial blush grade (MBG) 2 and 3 were 39 and 45%, respectively. Distal embolization was visible in three patients (4%) on the final angiogram.
At 30-days follow-up, two patients underwent target vessel revascularization (a re-PCI and a CABG) and no deaths or reinfarctions occurred.
Multivariate linear regression analysis demonstrated that "thrombus visible on initial angiography" was the only significant variable associated with increase in TIMI flow after thrombus aspiration (see Table II).

Table 2. Analysis of aspirated material

		Age (yrs)		Gender (Men)		MVD		Initial TIMI flow		Thrombus CAG*	
	Total	<60	≥60	no	Yes	no	yes	0/1	2/3	no	yes
Total , N	70	31	39	15	55	28	36	23	47	34	36
Effective thrombus aspiration, N (%)	58 (83%)	29 (94%)	29 (74%)	11 (73%)	47 (85%)	23 (82%)	30 (83%)	21 (91%)	37 (79%)	26 (76%)	32 (89%)
Thrombus											
White platelet thrombus	44 (76%)	72%	79%	82%	74%	70%	77%	57%	86%	92%	63%
Red erythrocyte-rich thrombus	14 (24%)	28%	21%	18%	26%	30%	23%	43%	14%	8%	38%
Plaque											
Thrombus with plaque comp	14 (24%)	28%	21%	9%	28%	22%	23%	33%	19%	15%	31%
Thrombus without plaque comp	44 (76%)	72%	79%	91%	72%	78%	77%	67%	81%	85%	69%
Size											
Small	37 (64%)	59%	69%	82%	60%	65%	63%	38%	78%	85%	47%
Medium	10 (17%)	17%	17%	9%	19%	17%	13%	29%	11%	8%	25%
Large	11 (19%)	24%	14%	9%	21%	17%	23%	33%	11%	8%	28%

*Thrombus visible on initial angiogram, Comp.= Component, MVD= Multivessel disease.

Histopathological Outcome

Thrombus aspiration was effective (retrieval of atherothrombotic material) in 58/70 patients (83%). With inclusion of the 13 patients in which thrombus aspiration was not attempted, the rate of effective thrombus aspiration is 58/83 patients (70%). Microscopic analysis of aspirated material showed white platelet thrombus in 44 patients (76%) and red erythrocyte-rich thrombus in only 14 patients (24%). Thrombi with plaque components were found in 14 patients (24%). The size of particles was small in 37 (64%), moderate in 10 (17%), and large in 11 patients (19%). The outcomes of the histopathological analysis in subgroups are detailed in Table III. In particular, the presence of thrombus on the initial angiogram and lower initial TIMI flow were associated with retrieval of large, erythrocyte rich, thrombotic particles.

DISCUSSION

In summary, this prospective study demonstrates the following: thrombus aspiration in NSTEMI is a safe method to prepare the culprit lesion for stent implantation; associated with a high rate of retrieval of thrombotic material; decreases intracoronary thrombus burden; and results in improved flow in the ischemiarelated coronary artery.
In high-risk ACS-patients with elevated troponin levels or ST-segment depression, an early invasive strategy has proven to be effective.[10,11] However, mobilization and subsequent embolization of thrombus and plaque material occurs in a majority of PCI procedures and plays a significant role in the pathogenesis of impaired reperfusion.[1,12] Especially in patients with non-ST-elevation ACS, PCI-induced distal embolization is of clinical importance, as reflected by the high incidence of periprocedural myocardial infarction in these patients.[13–15]
Recently, Galiuto et al. have demonstrated that thrombus aspiration in STEMI can significantly reduce the severity and extent of myocardial obstruction, as measured by contrast-enhanced echocardiography.[2] Several trials have demonstrated that thrombus aspiration significantly improves myocardial perfusion after primary PCI as assessed by myocardial blush grade and ST-segment elevation resolution.[4,16,17] The largest trial to date, the TAPAS-trial, evaluated the efficacy of thrombus aspiration compared with convention angioplasty in 1,071 patients undergoing PCI for STEMI. In this trial, thrombus aspiration resulted in improved myocardial perfusion and clinical outcomes.[4,5]

Table 3. Multivariate regression analysis of significant variables at univariate analysis (p<0.15)

	Effective thrombus aspiration		
	OR	95% CI	p
Thrombus visible pre	11.76	0.69 to 201.75	0.09
Number of vessels diseased	2.04	0.38 to 10.83	0.40
Heart rate at admission	1.14	1.01 to 1.28	0.040
Body Mass Index	0.77	0.58 to 1.02	0.07
	Delta pre and post aspiration TIMI flow		
	ARD	95% CI	p
Thrombus visible pre	0.89	0.39 to 1.39	0.001
Heart rate at admission	0.01	-0.01 to 0.03	0.19
Sex (male)	0.26	-0.36 to 0.87	0.41
Systolic Blood Pressure	-0.01	-0.02 to 0.00	0.09
Anterior MI	-0.30	-0.81 to 0.20	0.24

ARD = absolute risk difference, CI = confidence interval, GP = Glycoprotein IIbIIIa inhibitor, MI = Myocardial Infarction, n/a = not applicable, OR = Odds Ratio.

In this study, comparison of pre- and postthrombus aspiration angiograms demonstrated a marked improvement of coronary blood flow and reduction of thrombus load, indicating that thrombus aspiration is an effective method to prepare the culprit lesion for stent

implantation. The efficacy of thrombus aspiration was also indirectly confirmed by a high incidence of MBG 2/3, a low incidence of distal embolization, and a high rate of direct stenting.

Thrombus aspiration in NSTEMI was effective in a large majority of patients, comparable to the rate found in STEMI patients treated with this aspiration catheter.[4] Aspirated material contained predominantly white thrombi, as can be expected in patients with high initial epicardial flow (77% had TIMI-flow 1–3), in a pattern that shows remarkable similarity to findings in STEMI patients.[4] The presence of thrombus on the initial angiogram and lower initial TIMI flow were associated with retrieval of large, erythrocyte rich, thrombotic particles.

Compared with earlier reports on conventional PCI in non-ST-elevation ACS, the 30 days incidences of death, reinfarction, and revascularization in our study on thrombus aspiration are low.[13–15] For example, in the TACTICS-TIMI-18 study,[14] 2,220 patients with unstable angina (63%) or NSTEMI (37%) were randomized to an early invasive strategy (catheterization within 4–48 hr and PCI as appropriate) or to a more conservative treatment (catheterization only if the patient had objective evidence of recurrent ischemia or an abnormal stress test). Standard medical therapy included aspirin, heparin, and glycoprotein IIb/IIIa antagonists. The incidence of death or nonfatal reinfarction was 4.7% in the early invasive group and 7.0% in the conservative strategy at 30 days. In the subgroup of patients in the early invasive group who underwent PCI (41%) the incidence of death at 30 days was 1.9%. The TRITON-TIMI-38 study of Wiviott et al. randomized 13,608 patients who underwent PCI for ACS (26% STEMI and 74% unstable angina or NSTEMI) to prasugrel or clopidogrel. The incidence of glycoprotein IIb/IIIa antagonists use was 54%. The incidence of cardiac death, nonfatal reinfarction, or nonfatal stroke was ±5% in the prasugrel group and 67% in the clopidogrel group at 30 days (percentages retrieved from Kaplan-Meier curves). Inaddition, the ICTUS trial[13] randomized 1,200 patients with ACS without ST-segment elevation to an early invasive strategy or to a more conservative (selectively invasive) strategy. Patients received aspirin daily, enoxaparin for 48 hr, and a glycoprotein IIb/IIIa antagonist at the time of PCI. The mortality rate at 1 year was similar in the two groups (2.5%). Reinfarction rate at 1 year occurred in the 15% of the patients in early invasive management group and in 10.0% of the conservative group.

Thrombus aspiration seems to be safe in patients with NSTEMI, as no complications associated with thrombus aspiration occurred in this study. As also observed in the TAPAS trial, thrombus aspiration was demonstrated to be safe (no flow-limiting dissections) and a straightforward therapy (similar duration of fluoroscopy and door-to-balloon times as the control group).[4]

This single-center prospective cohort study on the impact of thrombus aspiration in NSTEMI suffers of several limitations, including a small sample size and absence of control group. In addition, thrombus aspiration was not attempted in 13 patients. With inclusion of these 13 patients in the analysis of the rate of effective thrombus aspiration, our success rate is 58/83 patients (70%). Randomized controlled trials are necessary to investigate if thrombus aspiration in NSTEMI results in improved angiographic and clinical outcomes when compared with conventional PCI.

In conclusion, this study demonstrates that thrombus aspiration in most NSTEMI patients is feasible and safe and is associated with a high rate of retrieval of thrombotic material.

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CHAPTER 10

Thrombus aspiration beneficial in ST-elevation myocardial infarction patients eligible for direct stenting

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ABSTRACT

Aim

To evaluate the additional effect of thrombus aspiration in ST-Elevation Myocardial Infarction (STEMI) patients who are eligible for direct stenting.

Methods and Results

Data were obtained from all consecutive STEMI patients treated with primary PCI from January 2004 to December 2007 in our hospital. Patients treated with direct stenting were compared to patients who received thrombus aspiration prior to stenting.
Of the 1992 STEMI patients, 751/1992 (37.7%) were eligible for direct stenting. Direct stenting was performed in 245/751 (32.6%) and thrombus aspiration prior to stenting in 506/751 (67.4%) patients. Despite worse angiographic baseline characteristics, thrombus aspiration prior to stenting was associated with significant improved primary endpoint Myocardial blush Grade (p=0.002) and TIMI flow grade (p=0.013) as compared with the direct stenting group. The beneficial contribution of thrombus aspiration prior to stenting to myocardial reperfusion remained after correction for well-known prognostic factors.

Conclusion

This study indicates that thrombus aspiration is of additional benefit in STEMI patients who are eligible for direct stenting.

INTRODUCTION

Several randomized controlled trials and meta-analyses have demonstrated that manual thrombus aspiration is associated with improved myocardial reperfusion as compared with conventional percutaneous coronary intervention (PCI) in patients with ST-Elevation Myocardial Infarction (STEMI).[1-4] These studies demonstrated that in patients with sufficient antegrade coronary flow after thrombus aspiration, balloon predilatation before stenting was often not necessary. This resulted in a higher rate of stenting without predilatation compared with conventional PCI. Since some studies suggest that direct stenting is superior compared with balloon predilatation followed by stenting,[5,6] the beneficial effect of thrombus aspiration could (partly) be related to the effect of direct stenting. It is currently unclear what the value is of direct stenting in the context of primary PCI, and whether thrombus aspiration is still beneficial in patients who are eligible for direct stenting.

In the present analysis, we compared STEMI patients who underwent direct stenting with patients who underwent thrombus aspiration prior to stenting in routine clinical practice.

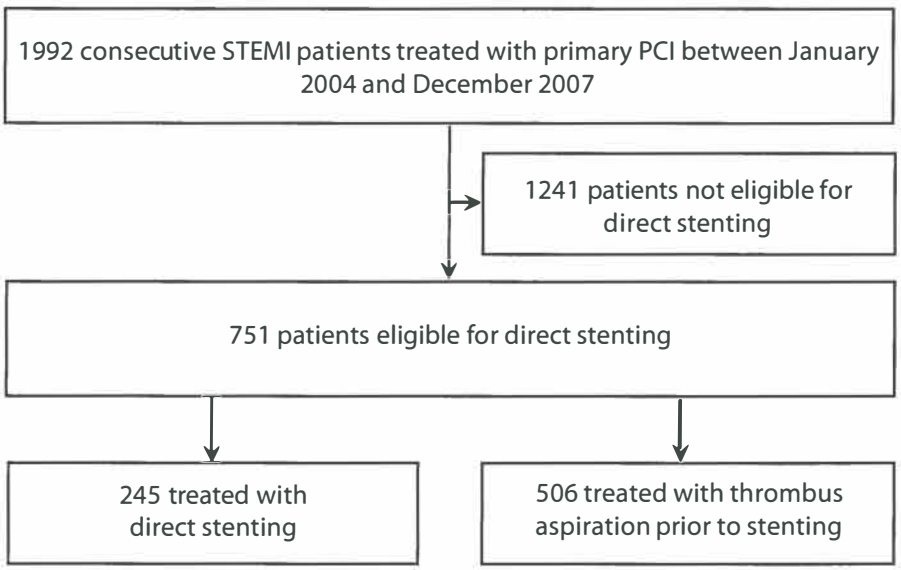

Figure 1. Flow diagram

METHODS

Patient selection

Patients treated with primary PCI for STEMI in the University Medical Center Groningen were included. Inclusion criteria were: ST-segment elevation >0.1mV in 2 or more leads on the ECG, onset of symptoms less than 12 hours or less than 24 hours with persisting symptoms due to ongoing ischemia, and eligible for direct stenting. Eligible for direct stenting included those patients in whom the operator decided that balloon predilatation was not necessary before stent implantation.
To investigate the additional benefit of thrombus aspiration prior to stenting in patients eligible for direct stenting, we compared patients undergoing direct stenting with patients receiving only thrombus aspiration prior to stenting. To limit selection bias, these two groups were selected from 2 different populations. The direct stenting group was selected from a population in which conventional PCI was the preferred strategy; patients treated from January 2004 until January 2005 and those randomized to conventional PCI in the context of the TAPAS[7] between January 2005 until December 2006. The thrombus aspiration group was selected from a population in which thrombus aspiration was the preferred strategy; patients treated after January 2007 (when thrombus aspiration became the preferred treatment) untill December 2007 and those randomized to thrombus aspiration in the context of the TAPAS.

Angiographic analysis

All coronary angiograms were analyzed by an independent core laboratory or by two experienced observers blinded to all clinical data. The sequence of intervention during PCI was determined on coronary angiogram. The myocardial perfusion was determined by the contrast density of the myocardial region of the infarct-related artery and classified as MBG 0: no myocardial blush or persisting blush (staining), 1: minimal myocardial blush, 2: moderate myocardial blush or 3: normal myocardial blush, all compared to the MBG of myocardial regions of non-infarct-related arteries.[8] Thrombolysis In Myocardial Infarction (TIMI) flow grade was classified as 0: no antegrade flow, 1: minimal antegrade flow into the obstructed segment, 2: slow antegrade flow into the distal bed, 3: normal antegrade flow into the distal bed.[9] Large thrombus burden was defined as TIMI thrombus grade 4 or 5.[10]

Endpoints

Primary endpoint of this study was MBG. Secondary endpoints were TIMI flow grade after PCI and all-cause mortality at 30 days and 1 year. Mortality was collected in all patients using municipal civil registries, which has completeness of vital status of all residents registered in The Netherlands.

Statistical analysis

Normally distributed continuous variables are presented as mean with standard deviation (SD) and were compared using a two-tailed Student's t-test. Skewed distributed continuous variables are presented as median with interquartile range (IQR) and were compared using a Mann Whitney U test. Categorical variables are presented as number

Table 1. Baseline characteristics

	Direct Stenting n=245	Thrombus aspiration prior to stenting n=506	P-value
General characteristics			
Age, years (mean±SD)	61.0±13	61.9±12	0.37
Male sex	169/245 (69)	364/506 (72)	0.40
History			
Hypertension	82/201 (41)	151/479 (32)	0.020
Diabetes mellitus	26/217 (12)	45/492 (9)	0.25
Hypercholesterolemia	65/206 (32)	95/416 (23)	0.019
Myocardial infarction	16/227 (7)	36/494 (7)	0.91
PCI	10/245 (4)	36/506 (7)	0.10
CABG	8/245 (3)	19/506 (4)	0.74
Current smoking	114/195 (58)	230/455 (51)	0.06
Ischemic time, minutes (median (IQR))	177 (125-245)	175 (130-255)	0.44
Angiographic characteristics			
Culprit location			0.15
Right coronary artery	95/245 (39)	205/506 (41)	
Left anterior descending artery	108/245 (44)	199/506 (39)	
Left circumflex artery	35/245 (14)	89/506 (18)	
Other	7/245 (3)	13/506 (3)	
Multivessel disease	145/242 (60)	315/505 (63)	0.50
TIMI flow grade pre			<0.001
0	58/242 (24)	228/504 (45)	
1	21/242 (9)	59/504 (12)	
2 or 3	163/242 (67)	217/504 (43)	
Visible thrombus	182/242 (75)	417/505 (83)	0.018
Large thrombus burden	107/240 (45)	318/502 (63)	<0.001
Reference vessel diameter <3mm	21/236 (9)	54/460(12)	0.25
Number of stents implanted (mean±SD)	1.2±0.6	1.3±0.6	0.40
Mean stent diameter (mean±SD)	3.3±0.6	3.3±0.7	0.93

Data are number (%) unless otherwise indicated. PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, TIMI = Thrombolysis In Myocardial Infarction, SD = standard deviation, IQR = interquartile range.

and percentage and were compared using the $\chi 2$ test. Multivariable regression analysis was used to evaluate the independent contribution of thrombus aspiration prior to stenting to MBG 3 after correction for baseline differences and well-known predictive variables. Statistical significance was defined as a two-sided p-value of less than 0.05. Statistical analysis was performed using SPSS software version 16.0 (SPSS, Chicago, USA).

RESULTS

Study population

In total, 1992 STEMI patients were treated with primary PCI in our hospital in the 4 year period. Of these patients 751 (37.7%) were eligible for direct stenting and were included in the present analysis. Direct stenting was performed in 245/751 (32.6%) patients and thrombus aspiration prior to stenting was performed in 506/751 (67.4%) patients (Figure 1). Patients who received thrombus aspiration prior to stenting had worse angiographic baseline characteristics, including lower TIMI flow grade and larger thrombus burden before PCI (Table 1).

Outcome

There was an significant increase of the primary endpoint MBG in the group of thrombus aspiration prior to stenting (MBG 0, 1, 2 and 3: 2%, 15%, 38% and 45%) compared to the group of direct stenting (7%, 14%, 41% and 38%) (p=0.002) (Table 2 and Figure 2). TIMI flow grade after PCI was also significant higher in the group of thrombus aspiration prior to stenting (TIMI 0, 1, 2 and 3: 0%, 1%, 9% and 91%) compared to the group of direct stenting (1%, 3%, 9% and 87%) (p=0.013)) (Table 3 and Figure 3). Multivariable analysis showed that thrombus aspiration prior to stenting was an independent predictor of MBG 3 after correction for age, ischemic time, anterior infarction, TIMI flow 0 or 1 and visible thrombus before PCI (Table 3). All-cause mortality at 30 days and 1 year was available in all patients and showed a trend in favour of thrombus aspiration prior to stenting (Table 2).

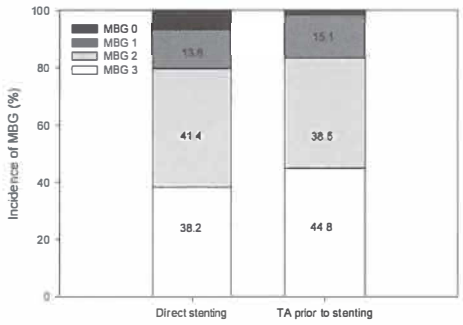

Figure 2. Incidence of the primary endpoint Myocardial Blush Grade after the procedure.

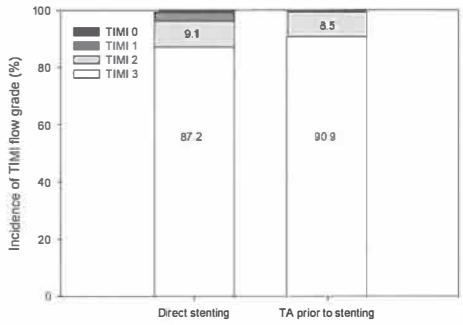

Figure 3. Incidence of TIMI flow grade after the procedure.

DISCUSSION

This study indicates that thrombus aspiration prior to stenting has additional benefit compared with direct stenting in STEMI patients undergoing primary PCI. Despite the worse TIMI flow grade and more visible thrombus before PCI, patients treated with thrombus aspiration prior to stenting had significant increased myocardial reperfusion.

Table 2. Outcome characteristics

	Direct Stenting n=245	Thrombus aspiration prior to stenting n=506	P-value
Post procedural characteristics			
MBG	n=220	n=491	0.002
0	15 (6.8)	8 (1.6)	
1	30 (13.6)	74 (15.1)	
2	91 (41.4)	189 (38.5)	
3	84 (38.2)	220 (44.8)	
TIMI flow grade	n=243	n=504	0.013
0	2 (0.8)	0 (0)	
1	7 (2.9)	3 (0.6)	
2	22 (9.1)	43 (8.5)	
3	212 (87.2)	458 (90.9)	
Follow-up			
30 days mortality	9 (3.7)	12 (2.4)	0.310
1-year mortality	16 (6.5)	21 (4.2)	0.158

Data are number (%). MBG = Myocardial Blush Grade, TIMI = Thrombolysis In Myocardial Infarction.

Furthermore, increased restoration of blood flow was observed in this study. Several suggestions can be made to explain the additional benefit of thrombus aspiration prior to stenting. Firstly, distal embolization occurs frequently in patients undergoing primary PCI and is associated with impaired myocardial reperfusion and poor clinical outcome.[11] It is likely that when thrombus burden is present, despite sufficient antegrade coronary flow, distal embolization is still at risk in patients treated with direct stenting. As thrombus aspiration reduces the atherothrombotic burden, it reduces the risk of distal embolization.[1,2] Further, the risk of distal embolization is thought to be highest during this first intervention, whether this is balloon dilatation or stent implantation. Therefore, also in patients eligible for direct stenting, a PCI strategy starting with thrombus aspiration before stenting is likely to result in less distal embolization as compared with those who undergo direct stenting.

Secondly, sufficient antegrade flow through the infarct-related segment is necessary for selection and positioning of the stent. As thrombus aspiration results in the majority of the patients in sufficient antegrade flow, balloon predilatation before stenting is often not necessary. In contrast, stenting in patients without sufficient antegrade flow has the risk of undersized stenting or inaccurate positioning of the stent, which are predictors for restenosis and stent thrombosis.[12,13]

Finally, the remaining fractured atherothrombotic burden after the PCI-procedure exposes thrombogenic contents. Restenosis and stent thrombosis are partly induced as a response to these contents.[14,15]

To the best of our knowledge, this study is the first that compares direct stenting with and without prior manual thrombus aspiration in routine clinical practice. Several studies have compared direct stenting with predilatation mainly in elective patients with variable findings.[5,6] In selected patients, direct stenting appears to be safe and possibly associated with improved clinical outcome. However, in unselected STEMI patients no improved myocardial perfusion or clinical outcome was detected.[16] In a recent randomized trial with selected STEMI patients, mechanical thrombus aspiration prior to stenting did not improve myocardial perfusion, but did improve longterm clinical outcome compared to direct stenting.[17]

Table 3. Contribution of thrombus aspiration prior to stenting to myocardial blush grade 3

	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Age (yr)	0.98 (0.96-0.99)	<0.001	0.98 (0.97-0.99)	0.001
Ischemic time	1.00 (1.00-1.00)	0.051	1.00 (1.00-1.00)	0.060
Anterior infarction	0.55 (0.45-0.68)	<0.001	0.54 (0.39-0.76)	<0.001
TIMI pre-PCI 0 or 1	0.62 (0.46-0.84)	0.002	0.72 (0.50-1.06)	0.093
Visible thrombus	0.54 (0.37-0.78)	0.001	0.62 (0.39-0.97)	0.037
TA prior to stenting	1.31 (0.95-1.82)	0.099	1.50 (1.05-2.14)	0.026

TA = thrombus aspiration, TIMI = Thrombolysis In Myocardial Infarction.

As described in these trials, patient selection in both interventions is inevitable. Stenting alone is not favourable in patients with large thrombus burden or low TIMI flow grade, for example. Because both angiographic characteristics are associated with worse prognosis, population bias for the choice of direct stenting or thrombus aspiration before stenting will always influence the benefit.

The main limitation of this study is the fact that direct stenting was not studied in a randomized fashion. However, we wanted to evaluate the treatment of patients who were eligible for stenting alone according to the operator in routine clinical practice. Furthermore, the size of the study is too small to detect significant differences in clinical outcome. We used myocardial blush grade as the surrogate end point, which is strongly associated with clinical outcome.[3,7,18]

CONCLUSION

This is the first study that evaluated the difference in outcome of STEMI patients treated with direct stenting compared to manual thrombus aspiration prior to stenting in routine clinical practice. Our study shows that thrombus aspiration prior to stenting has additional benefit compared with stenting alone on procedural outcome, despite the worse antegrade flow and thrombus burden before PCI.

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CHAPTER 11

Operator dependence of outcome after primary percutaneous coronary intervention

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ABSTRACT

Aims

Primary percutaneous coronary intervention (PCI) is a widely practised therapeutic procedure to treat ST-elevation myocardial infarction (STEMI). However, a significant proportion of patients undergoing primary PCI suffers from adverse events, such as incomplete myocardial reperfusion. It is currently unknown to which degree these adverse events are operator related.

Methods and results

We investigated inter-operator variation using objective safety and efficacy endpoints during primary PCI for STEMI. All PCI's were performed by six experienced interventional cardiologists as part of a randomised single centre trial. The primary endpoint of this study was optimal myocardial reperfusion (myocardial Blush grade 3 [MBG]). All 1,071 patients enrolled in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) were included in this analysis. In the six operator groups, the rate of the primary endpoint MBG3 ranged between 29.2% and 55.5%. The variable for operators remained significantly associated with MBG3 after adjustment for baseline and procedural differences. There were no statistical differences observed with regard to safety endpoints.

Conclusions

This study illustrates the observation that even in a controlled setting significant inter-operator variation may exist in the efficacy of primary PCI. This study supports the routine collection of high-quality datasets to evaluate and improve individual operator competence and skills.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a widely practised therapeutic procedure to treat coronary heart disease. In Europe, more than 1,100,000 PCIs are performed yearly, while in the United States that number is more than 1,300,000.[1,2] Due to rapid improvement and innovation of catheter techniques, devices and co-medication, PCI is nowadays considered safe and suitable as reperfusion therapy for patients with acute ST-elevation myocardial infarction (STEMI).[1-5] This is mainly based on the low incidence of major adverse cardiac and cerebral events (death, reinfarction, revascularisation and stroke) during and after primary PCI.[5,6]

However, a significant proportion of patients treated with primary PCI for STEMI suffer from more hidden, but nevertheless serious adverse events, such as bleeding requiring blood transfusion,[7-9] distal embolisation,[10-14] and incomplete myocardial reperfusion.[10,11,15] Although, patient related factors play a major role in the occurrence of these adverse events,[7-15] it is currently unknown to which degree these adverse events are also operator related.

Previous published studies and medical audits have investigated operator dependence of outcome after primary PCI with rates of inhospital mortality and/or other major adverse events as endpoints, and found almost no differences across operators.[6,16-21] As the incidences of these events are low, the analyses had limited statistical power to conclude whether there is significant operator dependence of outcome in the context of primary PCI. In addition, interpreting individual outcome data requires stratification of outcomes based on operator versus other factors, such as system of care, hospital quality, temporal factors, patient related factors, procedural characteristics and adjunctive therapies. Because of incomplete data sets, studies were often not able to fully adjust their data for possible confounders.[6,16,17,22] Finally, data collection and analyses were often not done by independent investigators, which may have induced bias in the reported results.[6,16-21]

We therefore thought to investigate inter-operator variation using objective safety and efficacy endpoints during primary PCI for STEMI. All PCI's were performed by six experienced interventional cardiologists as part of a large randomised controlled single centre trial.[23,24] All endpoints were analysed by a core laboratory or independent investigators.[25] The primary hypothesis was that even in the controlled setting of a randomised controlled trial with experienced interventional cardiologists, significant inter-operator performance variation exists in terms of efficacy and safety.

METHODS

The University Medical Center Groningen (UMCG) is a large tertiary referral centre in the northern part of The Netherlands. The UMCG has a high volume PCI centre with a 24-hour on-call duty schedule. Annually, around 2,000 PCIs (1,250 elective and 750 emergency PCIs) are performed by six interventional cardiologists: R.L. Anthonio, A.F.M. van den Heuvel, G.A. Jessurun, B.J. de Smet, E.S. Tan and F Zijlstra. All operators had a total individual case load of >1500 PCIs before the start of the study period. During the study period they all performed an annual number of >250 PCIs.

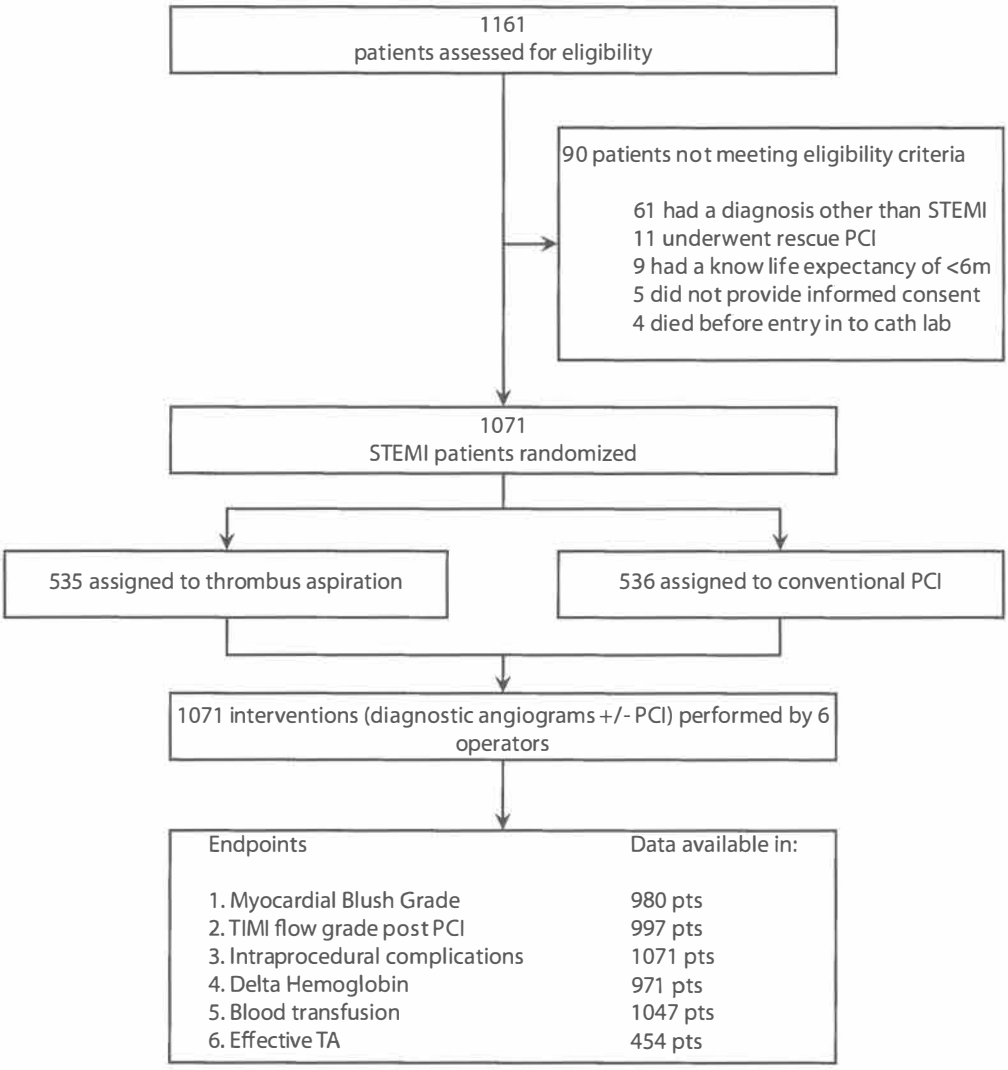

Figure 1. Trial Flow Diagram.

Patients

We included all 1,071 patients who were enrolled in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS). The study design, methods and results of the TAPAS-trial have been reported.[21-23] The TAPAStrial was a single-centre, prospective randomised open trial with blinded evaluation of endpoints, which investigated whether thrombus aspiration was superior to conventional treatment during PCI in patients with STEMI who were candidates for primary PCI. The

primary endpoint of the trial was post PCI myocardial blush grade (MBG).
All patients admitted to the UMCG during the study period were assessed for eligibility. The inclusion criteria were, symptoms suggesting acute myocardial ischaemia >30 minutes, time from symptom onset <12 hours, and ST-segment elevation >0.1 mV in two or more leads on the ECG. Exclusion criteria were rescue PCI after thrombolysis, known existence of a concomitant disease with life expectancy <6 months, and no informed consent.

Randomisation

Before initial coronary angiography, patients were randomly assigned in a 1:1 ratio to either thrombus aspiration or conventional treatment. Randomisation was done using a computerised voiceresponse system. The randomisation code was developed by means of a number generator used to select randomly permuted blocks of three to six patients. Randomisation was stratified by interventional cardiologists to achieve a balanced group assignment with regard to both treatment group and operator performing the PCI. All included patients were treated by one of the six interventional cardiologists. The name of the interventional cardiologist performing the procedure was prospectively registered in the main database.

Treatment

In patients randomised to thrombus aspiration, the Export Aspiration Catheter (Medtronic Corporation, Minneapolis, MN, USA) was used to establish antegrade flow before stenting. When necessary for stent delivery, balloon dilatation was performed before stenting. In conventional patients, balloon angioplasty was followed by stent placement. However, in both groups, the use of balloon dilatation as well as the use of (additional) stents was finally left over to the operators decision.
All patients were pre-treated with aspirin (a loading dose of 500 mg), heparin (5000 IU) and clopidogrel (loading dose of 600 mg), all administered directly after electrocardiographic confirmation of STEMI. Unless contraindicated, patients received weight-adjusted glycoprotein IIb/IIIa-inhibitor (GPI) abciximab) during the procedure and additional ACT-guided heparin. Arterial sheaths were removed with manual compression after PCI, no arterial puncture closing devices were used during the study period. Therapy after PCI was performed according to current guidelines.[4]

Quality evaluation and improvement programme

Our programme for quality evaluation and improvement was according to the guidelines of the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI).[18] Quality of care was assessed in weekly meetings in which interventional cardiologists and research fellows reviewed and evaluated all performed primary PCI's during that week (including all patients included in the TAPAS-trial). Two times a year, all complications occurring during PCI were discussed and evaluated. In addition, clinical follow-up of all patients undergoing PCI (STEMI and non-STEMI) in the UMCG were collected on a per operator basis and evaluated.

Endpoints

The primary endpoint was optimal myocardial reperfusion assessed by MBG. Secondary endpoints were effective thrombus aspiration, TIMI 3 flow post PCI, delta haemoglobin, the use of blood transfusions and intraprocedural complications. All endpoints were analysed by the core laboratory or independent blinded investigators.
MBG is a well established surrogate endpoint for myocardial reperfusion and is strongly related with death and other major adverse events after primary PCI.[15,23,24] Retrieval of thrombotic material after thrombus aspiration is an objective marker for efficacy of thrombus aspiration. Delta haemoglobin and the use of blood transfusions reflect bleeding complications during PCI. Bleeding complications are associated with longer hospital stays, higher health costs and may be also related with adverse outcome.[7-9]

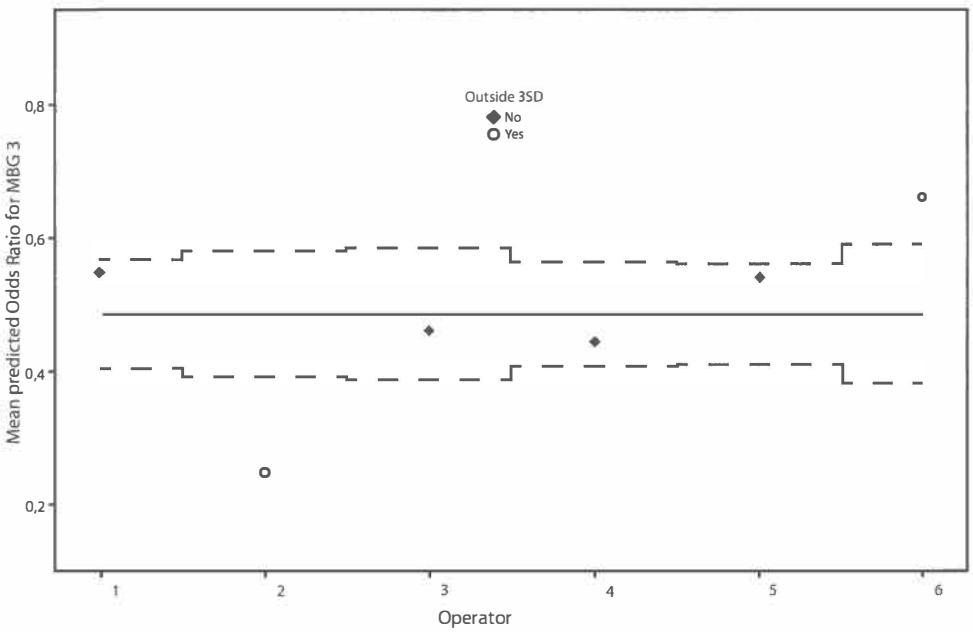

Figure 2. Control chart for odds ratio per operator for optimal myocardial perfusion after adjustment for baseline and procedural differences. Dotted lines represent 99.8% confidence intervals.

Endpoint assessment

MBG and TIMI flow grade were assessed as previously described.[15,26] All coronary angiographic data were analysed at an independent core laboratory (Cordinamo, Wezep, the Netherlands). Effective thrombus aspiration was determined by histopathological examination, performed by pathologists unaware of PCI-operator and clinical data.[25] Aspirated material during thrombus aspiration was placed in formalin, and fixed for 24 hours. Histological sections were cut and stained with hematoxylin-eosin for examination with a light microscope (x100). Samples were classified into effective or no effective

aspiration based on the presence of atherothrombotic material. Delta haemoglobin was calculated using the haemoglobin level at admission and one day after admission in patients who did not receive blood transfusions or underwent revascularisation (rePCI or CABG) within this period. The use of blood transfusions was defined as any gift of packed red blood cells given at the day of admission or one day after. Bleeding was subdivided in major and minor bleeding according the TIMI Bleeding Score.[26] Major Bleeding was defined as a reduction of haemoglobin of 5 g/dl or more from study entry to the time of the lowest haemoglobin level within 10 days. Minor Bleeding was calculated similar and was defined as a reduction of haemoglobin of 3 to 5 g/dl. Intraprocedural complications included intraprocedural deaths, strokes, CABG within 24 hours after diagnostic angiography, flow limiting dissections and side branch occlusions. We re-analysed all coronary angiograms and hospital records of patients who underwent CABG within seven days after diagnostic angiography, to investigate whether they were possibly related or caused by complications occurred during the index procedure.

Statistical analysis

Data are presented as frequency / number of patients with available data on the specific variable (percentage), mean ±SD or as median (interquartile range [IQR]). Comparisons across the six operator groups were performed by the Pearson chi-square test for categorical variables, one-way ANOVA for normal distributed continuous variables and Kruskal-Wallis test for not-normal distributed continuous variables. Multivariate regression analyses were used to correct for possible confounders. The following baseline variables were introduced in the multivariate analysis: age, gender, total ischemic time, diabetes, three vessel vessel disease, TIMI flow, previous myocardial infarction, systolic blood pressure and heart rate at admission, anterior myocardial infarction and off hour arrival at cathlab (to correct for differences in temporal factors, system of care before arrival and level of catheterisation lab staff occupation). In addition, the following procedural variables were used to correct for possible procedural differences: number of stents implanted, balloon used (both pre- and postdilatation), effective thrombus aspiration, GPI used and TIMI flow 3 post PCI. In the regression analyses, the categorical variable operator was coded using the simple contrast method; each operator (except the reference operator) was compared to the reference operator. The operator with the best performance for the primary endpoint was chosen as the reference operator. Predicted probabilities per patient after multivariate analysis were used to draw a control chart for the primary endpoint. All p-values were 2-tailed. Statistical significance was set at <0.002 (X3SD), because several studies have demonstrated that in the setting of comparing performance, a threshold of X3SD limits is more adequate to find special-cause variation in practice.[27,28] Analyses were performed using SPSS software version 16.0.1 (SPSS, Chicago, Il, USA).

Table 1. Baseline clinical and angiographic characteristics

Operator	#1	#2	#3	#4	#5	#6	p
Patients, N	209	152	158	169	233	150	
Age in years, mean ± SD	63.9 ± 12.9	63.5 ± 13.0	61.3 ± 12.4	64.0 ± 12.8	62.9 ± 12.5	62.3 ± 13.3	0.34
Male gender	147/209 (70.3)	107/152 (70.4)	119/158 (75.3)	114/169 (67.5)	160/233 (68.7)	108/150 (72.0)	
Body mass index, median (IQR)	26.2 (24.4 - 29.0)	26.8 (24.5 - 29.2)	26.1 (24.3 - 28.5)	26.2 (24.0 - 29.0)	26.3 (24.1 - 28.8)	27.0 (24.9 - 29.4)	0.40
Risk factors							
Diabetes	26/205 (12.7)	22/152 (14.5)	17/158 (10.8)	15/166 (9.0)	21/232 (9.1)	22/149 (14.8)	0.35
Hypertension	73/205 (35.6)	58/149 (38.9)	46/156 (29.5)	57/162 (35.2)	77/224 (34.4)	55/147 (37.4)	0.62
Hyperlipidemia	53/195 (27.2)	41/126 (32.5)	36/154 (23.4)	31/149 (20.8)	46/197 (23.4)	38/144 (26.4)	0.29
Family history	92/192 (47.9)	68/146 (46.6)	70/157 (44.6)	74/160 (46.2)	97/224 (43.3)	63/144 (43.8)	0.94
Previous CABG	5/206 (2.4)	2/151 (1.3)	8/158 (5.1)	10/166 (6.0)	7/232 (3.0)	7/149 (4.7)	0.19
Previous Myocardial infarction	20/206 (9.7)	12/151 (7.9)	14/158 (8.9)	20/166 (12.0)	23/232 (9.9)	18/148 (12.2)	0.78
Previous PCI	13/206 (6.3)	8/149 (5.4)	11/158 (7.0)	18/166 (10.8)	14/231 (6.1)	13/147 (8.8)	0.38
Hemodynamics pre-procedure, mean ± SD							
Systolic BP	129.4 ± 25.5	130.7 ± 26.8	126.6 ± 26.8	130.4 ± 25.9	128.0 ± 25.5	128.2 ± 26.9	0.73
Diastolic BP	74.6 ± 15.9	74.5 ± 17.1	74.8 ± 14.6	74.4 ± 15.7	73.5 ± 13.9	74.6 ± 15.5	0.96
Heart rate, beats/min	79.5 ± 19.3	78.6 ± 19.1	76.3 ± 15.1	76.4 ± 17.3	78.0 ± 17.9	81.9 ± 20.6	0.07
Total ischemic time in min, median (IQR)	180 (130 - 273)	180 (130 - 282)	182 (135 - 283)	195 (135 - 308)	195 (140 - 323)	190 (150 - 317)	0.46
Time of arrival at cath lab							
Off hours*	49/209 (23.4)	31/150 (20.7)	44/158 (27.8)	42/168 (25.0)	77/230 (33.5)	61/150 (40.7)	0.001
Three vessel disease	64/206 (31.1)	62/152 (40.8)	57/157 (36.3)	61/168 (36.3)	73/233 (31.3)	54/150 (36.0)	0.38
Infarct-related vessel							0.79
Left anterior descending artery	96/201 (47.8)	68/149 (45.6)	59/151 (39.1)	62/165 (37.6)	101/223 (45.3)	58/143 (40.6)	
Left circumflex artery	26/201 (12.9)	27/149 (18.1)	26/151 (17.2)	30/165 (18.2)	35/223 (15.7)	28/143 (19.6)	
Right coronary artery	75/201 (37.3)	53/149 (35.6)	61/151 (40.4)	69/165 (41.8)	81/223 (36.3)	54/143 (37.8)	
Other	4/201 (2.0)	1/149 (0.7)	5/151 (3.3)	4/165 (2.4)	6/223 (2.7)	3/143 (2.1)	
TIMI flow 0/1 pre procedure	119/208 (57.2)	90/151 (59.6)	88/154 (57.1)	92/166 (55.4)	142/232 (61.2)	73/146 (50.0)	0.39
Thrombus visible on initial angiogram	99/205 (48.3)	76/151 (50.3)	65/152 (42.8)	69/164 (42.1)	107/231 (46.3)	69/145 (47.6)	0.65

Data are presented as frequency / number of patients with available data on the specific variable (percentage).
* Weekdays from 5 pm to 7 am and any time on weekends. CABG= Coronary Artery Bypass Grafting, IQR= Interquartile range, SD= standard deviation, TIMI= Thrombolysis In Myocardial Infarction flow grade.

RESULTS

Only a minority (7.8%) of the patients assessed for eligibility, were excluded. The six operators each performed between 150 and 233 primary PCIs of the study. There were no differences in baseline clinical and angiographic characteristics across operator groups, except for the variable off hour arrival at catheterisation lab (Table 1).

Procedural variation

Procedural differences were present across operator groups with regard to the frequency of periprocedural GPI administration, use of balloon dilatation and stent implantation (Table 2).

Efficacy endpoints

Myocardial blush grade

MBG3 was present in 381/980 (38.9%) of the patients in which post PCI MBG could be assessed. In the six operator groups the rate of MBG3 ranged between 29.2% and 55.5% (Table 3). After adjustment for baseline and procedural characteristics in multivariate analysis, the variable operator remained a strong predictor of the primary endpoint MBG (Table 4).

Effective thrombus aspiration and TIMI flow 3 post PCI

Thrombus aspiration was effective in 331/454 (72.9%) patients. There was a significant difference in rate of effective thrombus aspiration between operator groups, ranging from 55.4% to 85.7%. No difference was found regarding post PCI TIMI flow 3 (Table 3).

Safety endpoints

Intraprocedural complications

The incidence of intraprocedural complications was low (see Table 3). No deaths, strokes or flow-limiting dissections occurred during the primary PCI procedures. A total of 29 patients underwent a CABG within seven days after diagnostic angiography. Thirteen (44.8%) of these CABGs were performed with 24 hours. None of the CABGs were caused by or related with intraprocedural complications. Side branch occlusions were visible in nine patients after stent implantation. No significant differences were present across operator groups with regard to these complications.

Bleeding complications

Data on delta haemoglobin was available in 971 patients. The median decrease in haemoglobin was 0.6 g/dL (IQR 0.2 to 1.3) (Table 3). Blood transfusions were given to 55/1047 patients (5.3%). No inter-operator variation was present regarding bleeding complications.

Table 2. Operator depended procedural characteristics

Operator	#1	#2	#3	#4	#5	#6	p
After diagnostic angiography:							0.13
No PCI performed	9/209 (4.3)	9/152 (5.9)	13/158 (8.2)	4/169 (2.4)	19/233 (8.2)	10/150 (6.7)	
Primary CABG performed							
<24 hours	2/209 (1.0)	3/152 (2.0)	1/158 (0.6)	0/169 (0.0)	1/233 (0.4)	0/150 (0.0)	
<7 days	3/209 (1.4)	4/152 (2.6)	3/158 (1.9)	0/169 (0.0)	1/233 (0.4)	2/150 (1.3)	
Primary PCI performed	200/209 (95.7)	143/152 (94.1)	145/158 (91.8)	165/169 (97.6)	213/233 (91.8)	140/150 (93.3)	
CABG performed after PCI							
<24 hours	1/209 (0.5)	0/152 (0.0)	2/158 (1.3)	1/169 (0.6)	0/233 (0.0)	2/150 (1.3)	
<7 days	3/209 (1.4)	1/152 (0.7)	5/158 (3.2)	3/169 (1.8)	1/233 (0.4)	3/150 (2.0)	
Procedural characteristics							
Thrombus aspiration performed	89/209 (42.6)	63/152 (41.4)	59/158 (37.3)	84/169 (49.7)	101/233 (43.3)	58/150 (38.7)	0.27
Balloon used	106/190 (55.8)	93/135 (68.9)	73/134 (54.5)	88/156 (56.4)	167/202 (82.7)	75/133 (56.4)	<0.0001
Stent implanted	186/189 (98.4)	126/136 (92.6)	119/134 (88.8)	148/159 (93.1)	185/203 (91.1)	116/134 (86.6)	0.002
Number of stents implanted, mean ± SD	1.3 ± 0.6	1.2 ± 0.7	1.3 ± 0.9	1.3 ± 0.7	1.2 ± 0.7	1.1 ± 0.6	0.032
Peri-procedural GPI	186/209 (89.0)	138/152 (90.8)	122/158 (77.2)	151/169 (89.3)	193/233 (82.8)	131/150 (87.3)	0.003
Intra-aortic balloon pump	8/194 (4.1)	5/137 (3.6)	11/125 (8.8)	14/154 (9.1)	8/202 (4.0)	12/137 (8.8)	0.07

Data are presented as frequency / number of patients with available data on the specific variable (percentage). CABG= Coronary Artery Bypass Grafting, GPI= Glycoprotein IIbIIIa inhibitor, IQR= Interquartile range, PCI= Percutaneous Coronary Intervention, SD= standard deviation, TIMI= Thrombolysis In Myocardial Infarction flow grade.

DISCUSSION

This analysis illustrates that even during primary PCI performed by experienced operators, and despite strict adherence to current guidelines in the setting of a randomised controlled trial, significant variation may exist with respect to the rate of optimal myocardial reperfusion. These differences remained significant after multivariate adjustment. There were no statistical differences observed with regard to safety endpoints.

It is currently a matter of discussion whether individual outcome data should be used as method to evaluate and improve the quality of heathcare. Important for this discussion is the availability of appropriate data to investigate the presence and impact of interoperator variation on procedural outcome. Our study setting allowed us to perform an accurate analysis on the impact of the operator on safety and efficacy. We investigated inter-operator variation in the setting of a randomised controlled single centre trial, therefore process of care, hospital quality and (co)therapy was comparable in all included patients. In

addition, as a result of the acute nature of primary PCI, operator specific outcome data was not influenced by operator dependent patient selection due to selective withholding or referral of procedures in patients at higher risk, this in contrast with previous analyses.[6,29,30] Previous studies investigated individual operator performance in terms of differences in mortality or other major adverse events.[6,16-21] For example, the New York State Department of Health reports risk adjusted mortality data for individual operators since 1994.6 Given the low in-hospital/30-day mortality rates (0.63% in non-emergency and 3.27% for emergency PCIs performed during 2003-2005) these analyses had often limited statistical power to detect interoperator differences. Further, as previously mentioned, data collection and analyses were often not done by independent investigators (in this case, the operator him or herself), which will have induced bias in the reported results.[6,16-21]

Table 3. Procedural outcomes and complications

Operator	#1	#2	#3	#4	#5	#6	p
Efficacy endpoints							
Myocardial Blush Grade							0.008
0	14/191 (7.3)	5/137 (3.6)	6/138 (4.3)	8/164 (4.9)	15/213 (7.0)	5/137 (3.6)	
1	28/191 (14.7)	32/137 (23.4)	25/138 (18.1)	27/164 (16.5)	35/213 (16.4)	13/137 (9.5)	
2	74/191 (38.7)	60/137 (43.8)	62/138 (44.9)	65/164 (39.6)	82/213 (38.5)	43/137 (31.4)	
3	75/191 (39.3)	40/137 (29.2)	45/138 (32.6)	64/164 (39.0)	81/213 (38.0)	76/137 (55.5)	
Effective Thrombus aspiration	74/89 (83.1)	45/63 (71.4)	40/59 (67.8)	72/84 (85.7)	56/101 (55.4)	44/58 (75.9)	<0.0001
TIMI 3 flow post PCI	163/197 (82.7)	123/142 (86.6)	121/139 (87.1)	132/165 (80.0)	179/214 (83.6)	122/140 (87.1)	0.42
Safety endpoints							
Deaths	0/209 (0.0)	0/152 (0.0)	0/158 (0.0)	0/169 (0.0)	0/233 (0.0)	0/150 (0.0)	1.00
Strokes	0/209 (0.0)	0/152 (0.0)	0/158 (0.0)	0/169 (0.0)	0/233 (0.0)	0/150 (0.0)	1.00
Emergency CABG	0/209 (0.0)	0/152 (0.0)	0/158 (0.0)	0/169 (0.0)	1/233 (0.4)	1/150 (0.7)	0.57
Flow limiting dissections	0/209 (0.0)	0/152 (0.0)	0/158 (0.0)	0/169 (0.0)	0/233 (0.0)	0/150 (0.0)	1.00
Side-branch occlusions	0/209 (0.0)	1/152 (0.7)	0/158 (0.0)	3/169 (1.8)	1/233 (0.4)	4/150 (2.7)	0.05
Bleeding complications							
Delta hemoglobin * [g/dL], median (IQR)	0.6 (0.0 - 1.1)	0.6 (0.0 - 1.1)	0.6 (0.0 - 1.1)	0.6 (0.0 - 1.1)	0.6 (0.3 - 1.5)	0.6 (0.0 - 1.4)	0.22
Blood transfusion †	7/207 (3.4)	9/151 (6.0)	10/150 (6.7)	7/163 (4.3)	14/230 (6.1)	8/146 (5.5)	0.72
Minor bleeding *	13/156 (7.7)	6/118 (4.6)	6/118 (4.6)	7/130 (5.1)	13/184 (6.6)	6/112 (5.1)	0.86
Major bleeding *	2/167 (1.2)	1/123 (0.8)	1/123 (0.8)	2/135 (1.5)	1/196 (0.5)	1/117 (0.8)	0.97

Data are presented as frequency / number of patients with available data on the specific variable (percentage).

* patients who received blood transfusions or underwent rePCI / CABG were excluded. † patients who underwent rePCI / CABG within the first days were excluded. CABG= Coronary Artery Bypass Grafting, IQR= Interquartile range, PCI= Percutaneous Coronary Intervention, SD= standard deviation, TIMI= Thrombolysis In Myocardial Infarction flow grade.

Analyses on clinical endpoints are certainly mandatory, however they should be accompanied with objective and sensitive surrogate endpoints. MBG and the secondary endpoints used in our study are important markers for efficacy and safety during primary PCI, and were analysed by either a core lab or blinded investigators. These endpoints are simple and not time consuming to collect and analyse, and therefore useful for evaluation of every day practice. In addition, the recent introduction of software for computer-assisted assessment of MBG and ST-segment resolution, further facilitates the routine use of these surrogate endpoints for assessing efficacy of reperfusion therapies.[31,32]
So what are the possible explanations of the observed inter-operator variation in efficacy? We adjusted for possible differences in patient case mix, temporal factors and process of care (e.g., total ischaemic time; on- versus off-hours).[22] The residual variation suggests difference in operator performance. Well investigated is the idea that the experience of an interventional cardiologist (operator volume) is inversely proportional to the incidence of procedure related complications during PCI.[18-21] However, it is not likely that "experience" played a major role in our study, as all operators were experienced and performed >250 PCIs/year. Further, there can be differences in opinions about the optimal approach during primary PCI. This may have caused inter-operator variation with regard to the use of co-medication, balloon dilatation and coronary stents. Several studies have demonstrated that the extent and the complexity of the procedure (higher number, duration, and pressure of balloon inflations and stent implantations) is associated with the occurrence of distal embolisation and impaired myocardial reperfusion.[10-14] The additional analyses performed in our study suggest that these procedural differences may partly explain the

Table 4. The effect of the operator on the primary endpoint optimal myocardial reperfusion (Myocardial Blush Grade 3)

	Operator effect on optimal myocardial reperfusion							
	Unadjusted		Adjusted for baseline variables†		Adjusted for procedural differences‡		Adjusted for both baseline and procedural differences	
	OR	99.8%CI	OR	99.8%CI	OR	99.8%CI	OR	99.8%CI
Operator 1 *	0.519	0.257 - 1.046	0.483	0.219 - 1.067	0.608	0.160 - 2.317	0.655	0.145 - 2.960
Operator 2 *	0.331	0.151 - 0.727	0.313	0.130 - 0.753	0.153	0.034 - 0.684	0.194	0.039 - 0.977
Operator 3 *	0.388	0.179 - 0.841	0.331	0.139 - 0.787	0.433	0.104 - 1.807	0.398	0.083 - 1.915
Operator 4 *	0.514	0.249 - 1.062	0.445	0.195 - 1.016	0.426	0.111 - 1.636	0.361	0.080 - 1.638
Operator 5 *	0.493	0.248 - 0.979	0.463	0.214 - 0.999	0.823	0.215 - 3.153	0.805	0.184 - 3.528
Operator 6 (reference)	-	-	-	-		-		

* Versus operator 6.

† Adjusted for the following baseline variables: age, gender, total ischemic time, diabetes, three vessel vessels disease, TIMI flow 0/1 pre, previous myocardial infarction, systolic blood pressure at admission, heart rate at admission, Time of arrival at cath lab (on versus off hours) and anterior myocardial infarction.

‡ Adjusted for the following procedural differences: number of stents implanted, balloon used (yes/no), effective thrombus aspiration, GP IIbIIIa inhibitor used (yes/no), TIMI flow 3 post procedure.

OR is for the occurrence of optimal myocardial reperfusion for the specific operator as compared with reference operator.

under/above performance of some operators. However, also after multivariate correction for procedural characteristics (including effective thrombus aspiration) there remained significant inter-operator variation with regard to impaired myocardial reperfusion. This suggest that differences in factors for which we were not able to account for, including most likely differences in technical skills, have contributed to the observed inter-operator variations.

The ACCF/AHA/SCAI Clinical Competence Statement 2007 proposes interventionalists to participate in local, regional and/or national PCI registries to monitor and improve both hospital and individual operator performance.[18] Our results strongly support this recommendation and demonstrate that the systematic collection, reviewing and reporting of data provides important feedback with regard to safety and efficacy of health care, and is mandatory even among experienced operators. Further, essential requisites for the investigation of inter-operator variation is the careful selection of endpoints and high quality data sets, collected and analysed by independent investigators.

Limitations

Our study suffers from several limitations: With regard to the operator, we did not adjust for differences in physician characteristics (age, years of experience and total caseload). In our opinion this is not necessary, as all operators had a sufficient total case load and number of PCIs performed per year to label them as experienced and assume that learning curves have flattened out. Secondly, we adjusted for important baseline and procedural characteristics. However, we can not rule out that our results were influenced by other confounders (such as quality of care before arrival at our hospital, experience of catheterisation staff, etc.). Thirdly, although all operators had trained with thrombus aspiration before the start of the study period – and we corrected for effective thrombus aspiration in additional analyses – the use of new devices such as thrombus aspiration may have augmented the observed inter-operator variation in this study. Finally, inter-operator variation was investigated only in terms of functional endpoints. However, as the magnitude of the inter-operator variation in our study is comparable with the effect size of thrombus aspiration on myocardial reperfusion in TAPAS (MBG3 rate was 32.2% in conventional PCI versus 45.7% in the aspiration group),[23] the impact of operator variation during primary PCI is certainly of clinical relevance.

CONCLUSION

Our study illustrates that even in a very controlled setting significant inter-operator variation may exist in the efficacy of primary PCI for STEMI. This study supports the routine collection, reporting and reviewing of high-quality datasets to evaluate and improve individual operator performance.

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CHAPTER 12

Summary

Part I Strategies for inducing and sustaining epicardial reperfusion

Restenosis

In chapter 2 the safety and efficacy of drug-eluting stents (DES) in patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) were investigated. In this registry study, the use of DES in a cohort of 552 STEMI patients was associated with an excellent event-free survival rate of 90.1% at 1 year post-discharge. In comparison with a historical cohort of 577 STEMI patients treated with bare metal stents (BMS), DES implantation was associated with a significant lower rate of target lesion revascularisation at follow-up. No significant difference in death or reinfarction was observed between the two types of stents.

These results and those of current published randomized controlled trials (RCT), indicate that DES are able to reduce in-stent restenosis and clinical recurrence at long term follow-up in patients with STEMI.[1-5] However, do these results also indicate that DES should be used routinely in all STEMI patients? A subanalysis of the largest RCT on DES versus BMS in STEMI (n=3006) suggests that DES are mainly effective in patients with a small vessel diameter (<3mm), long lesion length (≥30mm) and insuline-treated diabetes.[5] In patients without one of these risk factors (n=947/3006, 32.2%), no difference in target lesion revascularisation at 1 year was found between DES and BMS (3.3% versus 3.2%, p = 0.93). Further, there remain safety concerns, as DES in STEMI may be associated with an increased risk on late stent thrombosis. Several risk factors are identified for the occurrence of stent thrombosis, and the clinical presentation STEMI yields a considerable number of these.[6-9] In addition, in the acute phase of STEMI it is often unclear if patients have contraindications for extended dual antiplatelet therapy. Although the baseline risk on stent thrombosis for DES in STEMI is likely to be increased, RCTs and meta-analyses did not find a higher incidence of stent thrombosis associated with DES.[1-5]

Current data indicate that DES should not be used routinely. For each patient the benefit of less restenosis should be carefully weighed against the increased risk on stent thrombosis and higher costs. Finally, current published RCTs on DES versus BMS in STEMI investigated mainly older generation DES. Numerous new types of stents are currently being tested, focussing on higher efficacy and better safety profiles.[10]

Thrombotic complications

In chapter 3 the incidence of initial coronary artery patency and short-term outcome was compared in treatment groups of RCTs in which patients received pretreatment with clopidogrel with those in which patients did not receive clopidogrel before initial coronary angiography. A total of 38 treatment groups comprising 8429 patients was included. Initial patency and clinical outcome (death or non-fatal reinfarction) were found to be improved in treatment groups that received pretreatment with clopidogrel.

These findings are accordance with the experience of pretreatment with clopidogrel in elective patients, non–ST-elevation coronary syndromes, and thrombolytic studies.[11,12] Recently, the preliminary results of the first RCT on pretreatment of clopidogrel in patients undergoing primary PCI for STEMI were presented.[13] This trial randomized 337 patients

to pretreatment (n=166) or post-angiography clopidogrel 600mg loading dose (n=171). The preliminary results showed an increase in initial patency in the pretreatment group and lower rate of death or non-fatal reinfarction (1.2% versus 4.2%), without an increase of major bleeding (8.6% versus 8.2%) or stroke (0.0% versus 0.0%). These results indicate that it is safe and effective to give a loading dose of clopidogrel in patients as early as possible after ECG confirmation of STEMI. The relative merits of new type ADP-inhibitors are currently being investigated in several RCTs.

Multivessel disease

In Chapter 4 the composite published data on the 3 current PCI strategies for multivessel disease in STEMI patients were studied. Pairwise and network meta-analyses were performed of all published data to summarize current evidence for these 3 PCI strategies. Eighteen published studies, involving 40,280 patients, were included. Pairwise meta-analyses demonstrated that staged PCI was associated with significant lower short- and long-term mortality rates compared to culprit vessel only PCI and multivessel PCI. In addition, culprit vessel only PCI was superior at both short- and long-term follow-up compared to multivessel PCI. In the network analysis, staged PCI was also consistently associated with lower mortality rates compared to culprit vessel only PCI and multivessel PCI.
These analyses suggest that the possible benefits of multivessel PCI do not outweigh the adverse effects associated with this aggressive strategy. As advised in current guidelines, significant non-culprit vessel lesions suitable for PCI should only be treated during staged PCI procedures. More prospective research should be performed to investigate which strategy is superior, in both hemodynamic stable and unstable, STEMI patients (CABG versus culprit vessel only PCI versus staged PCI versus multivessel PCI).

Part II Strategies for improving microvascular reperfusion after primary PCI

Manual thrombus aspiration in STEMI

In chapter 5 the main results of the Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) are presented, which randomized 1071 patients to thrombus aspiration (n=535) or conventional PCI (n=536). The primary endpoint was optimal myocardial reperfusion (measured by myocardial blush grade [MBG] 2/3), which was significantly higher in the group treated with thrombus aspiration. This RCT demonstrated that thrombus aspiration is safe and applicable in a large majority of STEMI patients, and results in better myocardial reperfusion than conventional PCI. In chapter 6 it was investigated if the improvement in myocardial reperfusion associated with thrombus aspiration in the TAPAS, also translated into improved clinical outcome at one year follow-up. Compared with conventional PCI, thrombus aspiration before stenting of the infarct related artery seems to improve the 1-year clinical outcome after PCI for STEMI Currently, manual thrombus aspiration is increasingly used in routine clinical practice as it is an easy, relatively inexpensive and safe method to reduce thrombus burden and

improve myocardial reperfusion. Although several thrombus aspiration RCTs and meta-analyses also found an improvement in clinical outcome,[14-17] no RCT have been published which was adequately powered on a clinical endpoint. Currently, a multicenter RCT on thrombus aspiration is being performed which will randomize 5000 STEMI patients to either thrombus aspiration or conventional PCI.[18] As it is powered on 30 day all-cause mortality, this RCT will be able to answer the question if thrombus aspiration is also able to significantly improve survival.

The study in chapter 7, investigated what independent predictors are of effective thrombus aspiration in patients treated with routine thrombus. A total of 1712 patients underwent routine thrombus aspiration, which was effective in 82.6%. Multivariate independent predictors of effective thrombus aspiration were reference vessel diameter (>3mm), angiographic visible thrombus and total ischemic time (>3 hours). However, the discriminative value of these predictors together was low. This analysis demonstrated that routine manual thrombus aspiration in STEMI patients is feasible and results in successful thrombus retrieval in the majority of the patients.

Discussion remains if the presence of visible thrombus or other baseline characteristics should be used as a guide to perform thrombus aspiration. In the TAPAS study, subanalyses did not demonstrate significant differences in clinical benefit of thrombus aspiration across prespecified subgroups (TIMI flow, age, sex, total ischemic time, infarct related vessel, proximal lesion and thrombus seen on initial angiogram).[19] Also in a recent meta-analysis of individual patient data of most thrombus aspiration trials, no differences were found across these subgroups or other baseline patient characteristics.[14] These findings, together with the observed high efficacy rates across all patient subgroups in this study, support a strategy of routine thrombus aspiration over a more selective approach.

In chapter 8 the results of a prospective cohort study are shown. This study investigated whether a large-lumen-diameter catheter is superior in removing thrombus load and improving angiographic and electrocardiographic outcome compared to a medium-sized catheter. A total of 160 patients, treated with the Diver (n = 80) or Export (n = 80) aspiration catheter, was enrolled. No significant difference was found in rate of effective thrombus aspiration, MBG or electrocardiographic outcome between the 2 devices. Size distribution of retrieved thrombotic particles was similar per device.

This study indicates that a larger internal lumen diameter does not result in retrieval of larger thrombotic particles, nor in improved angiographic or electrocardiographic outcomes. The nonsuperiority of a larger-lumen catheter may be explained by the fact that freshly formed thrombi are easily friable. Further, it could also be related with better handling characteristics of medium-sized catheters. When evaluating all the different adjunctive mechanical devices to prevent distal embolisation, the best results are achieved with the most simple and easy to use devices.[20,21] Besides larger lumen diameter, also mechanic thrombus aspiration seems to be an interesting concept to improve thrombus removal. Several RCTs have been performed comparing mechanic thrombus aspiration with conventional PCI, however with conflicting and less convincing results.[22-24] Nevertheless, no direct comparisons have been performed between manual and mechanic thrombus aspiration, so it is currently unclear if manual is superior to mechanic thrombus aspiration.

Manual thrombus aspiration in NSTEMI

In chapter 9 the results of a prospective cohort study are presented, in which the feasibility and safety of thrombus aspiration during PCI for NSTEMI were investigated. Thrombus aspiration was effective in 58 patients (83%) and resulted in a marked reduction of TIMI-thrombus score and increase of the rate of TIMI-flow.
This study demonstrates that thrombus aspiration in most NSTEMI patients is feasible and safe and is associated with a high rate of retrieval of thrombotic material. Currently the efficacy of thrombus aspiration in patients with NSTEMI is investigated in the Thrombus Aspiration during Percutaneous coronary intervention in Acute non-ST-elevation myocardial infarction Study (TAPAS II).[25] This study will include 540 patients with acute NSTEMI who are candidates for urgent PCI. Patients are randomised to treatment with manual thrombus aspiration or to conventional PCI. The primary endpoint is the incidence of MBG 3 after PCI.

Direct stenting

In chapter 10, patients treated with direct stenting were compared to patients who received thrombus aspiration prior to stenting. A total of 751 patients was eligible for direct stenting. Direct stenting was performed in 32.6% and thrombus aspiration prior to stenting in 67.4% of the patients. Despite worse angiographic baseline characteristics, thrombus aspiration prior to stenting was associated with significant improved primary endpoint MBG and TIMI flow compared to the direct stenting group. The benefit of thrombus aspiration prior to stenting remained significant after correction for well-known prognostic factors.
These findings support the hypothesis that when thrombus is present, even in spite of normal antegrade epicardial flow, distal embolisation is still a risk in patients undergoing primary PCI. As thrombus aspiration reduces thrombus burden, it reduces the risk of distal embolisation.[14,26,27] Further, the risk of distal embolisation is thought to be highest during this first intervention, as well during balloon dilatation as stent implantation. Therefore, also in patients eligible for direct stenting, a PCI strategy starting with thrombus aspiration is likely to result in less distal embolisation and improved myocardial reperfusion compared to stenting.

Impact of the operator on microvascular reperfusion

In chapter 11 the presence and extend of inter-operator variation during primary PCI for STEMI was investigated using objective safety and efficacy endpoints. The primary endpoint was incidence of optimal myocardial reperfusion after primary PCI. All PCIs were performed by six experienced interventional cardiologists as part of the TAPAS. The primary endpoint of this study was optimal myocardial reperfusion (MBG 3). In the six operator groups the rate of the primary endpoint MBG 3 ranged between 29.2% and 55.5%. The variable operator remained significantly associated with MBG 3 after adjustment for baseline and procedural differences. There were no statistical differences observed with regard to safety endpoints.

This study makes evident that even in a controlled setting significant interoperator variation exists in the efficacy of primary PCI. This study supports the routine collection of high-quality datasets to evaluate and improve individual operator competence and skills.

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Summary in Dutch
Samenvatting in het Nederlands

Een acuut ST-elevatie myocard infarct (STEMI) wordt geïnitieerd door het openscheuren van een atherosclerotische plaque, waarna door blootstelling aan het bloed een trombus ontstaat, die het bloedvat gedeeltelijk of volledig afsluit. Afsluiting van het bloedvat leidt tot ischemie van het myocard. Snel herstel van de epicardiale en microvasculaire bloeddoorstroming na een ischemische periode is essentieel voor de beperking van schade aan het myocard. De laatste jaren is gebleken, dat een percutane coronaire interventie (PCI) de beste reperfusie therapie is bij patiënten met een STEMI.
Tijdens een PCI wordt de bloeddoorstroming door een afgesloten bloedvat hersteld door deze te dilateren. Echter, deze dilatatie zorgt ook voor compressie en fragmentatie van de atherosclerotische plaque en trombus. Deze beschadiging is verantwoordelijk voor de belangrijkste complicaties tijdens en na PCI; restenose, stent trombose en distale embolisatie. Het doel van dit proefschrift is om nieuwe strategieën te onderzoeken om deze PCI-gerelateerde complicaties te verminderen en zo de epicardiale en microvasculaire reperfusie te verbeteren.

Part I Strategieën voor het induceren en behouden van epicardiale reperfusie.

Restenose

In hoofdstuk 2 wordt de veiligheid en effectiviteit van medicijn-afgevende stents (drug-eluting stents, DES) onderzocht in patiënten, die een PCI ondergingen voor een STEMI. In deze registratie studie was het gebruik van DES geassocieerd met uitstekende 1-jaars resultaten. In vergelijking met patiënten, die behandeld werden met niet-medicijn-afgevende stents, gaf het gebruik van DES een significante afname van het aantal revascularisaties. De resultaten van deze studie tonen aan, dat DES ook in patiënten met een STEMI effectief zijn om restenose te verminderen. Echter, het is de vraag, of DES standaard gebruikt moeten worden in alle patiënten met een STEMI. Subanalyses van gerandomiseerde studies laten namelijk zien, dat DES maar in een deel van de patiënten effectief zijn. Tevens zijn er twijfels over de veiligheid van DES in STEMI, vooral in verband met een mogelijk verhoogd risico op stent trombose. Op basis van de huidige data kan dan ook niet geadviseerd worden om DES standaard te gebruiken in alle patiënten met STEMI. Per patiënt moet het voordeel van minder restenose afgewogen worden tegen een mogelijk hoger risico op stent trombose en hogere kosten van DES. Momenteel zijn diverse nieuwe stents in ontwikkeling, die mogelijk effectiever en veiliger zijn.

Trombotische complicaties

In hoofdstuk 3 wordt onderzocht, of voorbehandeling met een startdosis clopidogrel leidt tot een hogere incidentie van vroege epicardiale reperfusie en een betere klinische uitkomst ten opzichte van het pas geven na de PCI. Een systematische evaluatie van de huidige literatuur toonde aan dat STEMI patiënten, die een primaire PCI ondergingen en voorbehandeld werden met een startdosis clopidogrel, vaker vroege epicardiale reperfusie hadden en het klinisch beter deden dan patiënten die niet voorbehandeld werden. Deze bevindingen zijn in lijn met ervaringen van clopidogrel voorbehandeling

in andere patiënten groepen. Recent zijn de voorlopige resultaten van de eerste gerandomiseerde studie over clopidogrel voorbehandeling in patiënten, die een primaire PCI voor STEMI moeten ondergaan, gepubliceerd. Deze studie randomiseerde 337 patiënten naar clopidogrel voorbehandeling (n=166) of niet (n=171). De voorlopige resultaten toonden een toename in vroege reperfusie aan in de voorbehandelde groep en een lagere incidentie van sterfte en reinfarcten (1.2% versus 4.2%). Er werd geen toename gezien in bloedingen (8.6% versus 8.2%) of cerebrale vasculaire accidenten (0.0% versus 0.0%). Deze resultaten tonen aan, dat het veilig en effectief is om zo spoedig mogelijk na de electrocardiografische diagnosestelling van een STEMI een startdosis clopidogrel te geven. De relatieve voordelen van nieuwe type ADP-inhibitoren worden momenteel onderzocht in verschillende gerandomiseerde studies.

Meervatslijden

Meer dan de helft van de patiënten, die zich presenteren met een STEMI, heeft naast een vernauwing in het infarct gerelateerde vat ook 1 of meer bijkomende vernauwingen in andere kransslagvaten. Als het infarct gerelateerde vat behandeld is, kunnen bijkomende vernauwingen in andere kransslagvaten volgens 3 verschillende strategieën behandeld worden: (1) conservatief, (2) tijdens een tweede gestadieerde PCI of (3) direct tijdens de acute PCI (zgn. meervats-PCI). In hoofdstuk 4 worden op basis van de bestaande literatuur deze 3 strategieën voor meervatslijden in patiënten met STEMI met elkaar vergeleken. Paarsgewijze en netwerk meta-analyses werden verricht van alle gepubliceerde data over deze 3 strategieën. Achttien studies met in totaal 40.280 patiënten werden geïncludeerd. De paarsgewijze meta-analyses toonden aan, dat een gestadieerde PCI van bijkomende letsels geassocieerd was met significant betere korte en lange termijn overleving ten opzichte van een conservatieve strategie of een meervats-PCI. Verder bleek een conservatieve strategie gerelateerd aan een betere korte en lange termijn overleving ten opzichte van een meervats-PCI. Ook in de netwerk analyse was een gestadieerde PCI geassocieerd met betere overleving dan de conservatieve strategie of meervats-PCI.
Deze analyses suggereren, dat de mogelijke voordelen van een meervats-PCI niet opwegen tegen de negatieve effecten (met name een hoger complicatie risico) van deze agressievere strategie. Zoals ook geadviseerd in de huidige richtlijnen, dienen significante bijkomende vernauwingen, die geschikt zijn voor een PCI enkel behandeld te worden met een gestadieerde PCI. Echter, meer prospectief onderzoek moet verricht worden om verder te onderzoeken, welke van deze strategieën superieur is, in zowel hemodynamisch stabiele als instabiele STEMI patiënten.

Part II Strategieën om de microvasculaire reperfusie na primaire PCI te verbeteren.

Manuele trombus aspiratie in STEMI

In hoofdstuk 5 worden de hoofdresultaten van de Trombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) gepresenteerd. Deze studie randomiseerde 1071 patiënten met een STEMI na een behandeling met trombus

aspiratie (n=535) of conventionele PCI (n=536). Het primaire eindpunt was optimale microvasculaire reperfusie (gedefinieerd als myocardial blush grade 2/3), welke significant hoger was in de groep die behandeld werd met trombus aspiratie. De TAPAS toonde aan, dat trombus aspiratie veilig en toepasbaar is in de meerderheid van de patiënten met een STEMI en in een betere microvasculaire reperfusie resulteert dan conventionele PCI. In hoofdstuk 6 wordt onderzocht, of deze verbetering in microvasculaire reperfusie in de trombus aspiratie groep zich ook vertaalde in een betere klinische uitkomst na een jaar follow-up. Vergeleken met conventionele PCI leek trombus aspiratie in de TAPAS geassocieerd met een verbetering van de 1-jaars klinische uitkomst.
Manuele trombus aspiratie wordt momenteel in toenemende mate gebruikt tijdens de behandeling van STEMI. Dit omdat het een eenvoudig, goedkope en veilige methode is om trombus te verwijderen en de microvasculaire reperfusie te verbeteren. Naast een verbetering in microvasculaire reperfusie hebben verscheidende gerandomiseerde studies en meta-analyses ook een verbetering in klinische uitkomst gevonden. Echter, er zijn er tot op heden geen gerandomiseerde studies gepubliceerd, die specifiek ontworpen en groot genoeg waren om een verschil in een klinisch eindpunt te kunnen detecteren. Momenteel loopt er een gerandomiseerde multicenter studie, die het effect van trombus aspiratie versus conventionele PCI zal onderzoeken in 5000 STEMI patiënten. Aangezien het primaire eindpunt van deze studie een klinisch eindpunt betreft (sterfte na 30 dagen) zal deze studie meer duidelijkheid kunnen verschaffen, of trombus aspiratie ook in staat is om de klinische uitkomst significant te verbeteren.
In hoofdstuk 7 wordt onderzocht, wat de voorspellers waren van succesvol verwijderen van trombus met trombus aspiratie (effectieve trombus aspiratie). In totaal ondergingen 1712 patiënten trombus aspiratie, wat in 82,6% van de gevallen resulteerde in effectieve trombus aspiratie. Multivariabele voorspellers van effectieve trombus aspiratie waren arteriediameter (> 3mm), angiografisch zichtbare trombus en totale ischemische tijd (> 3 uur). Echter, de discriminerende waarde van deze voorspellers samen was laag.
Er blijft discussie, of trombus aspiratie standaard in alle patiënten verricht moet worden of slechts in een meer selectieve populatie. In de TAPAS waren geen significante verschillen in effectiviteit van trombus aspiratie in de verschillende subgroepen (gemaakt op basis van initiële epicardiale bloeddoorstroming, leeftijd, geslacht, totale ischemische tijd, infarct locatie, proximale laesie en angiografisch zichtbare trombus). Ook in een recente meta-analyse van individuele patiëntgegevens van de meeste trombus aspiratie studies werden geen verschillen in effectiviteit gevonden tussen deze subgroepen of andere baseline kenmerken van patiënten. Deze bevindingen, samen met de waargenomen hoge incidentie van effectieve trombus aspiratie in alle patiëntengroepen, ondersteunen een strategie van routine trombus aspiratie in plaats van een meer selectieve aanpak.
In hoofdstuk 8 werden de resultaten van een prospectieve cohort studie getoond, waarin onderzocht werd, of een trombus aspiratie katheter met een grotere diameter van het aspiratie lumen beter in staat is om trombus te verwijderen dan een katheter met een kleiner lumen. Tevens werd onderzocht, of een groter lumen resulteerde in een betere angiografische en electrocardiografische uitkomst. In totaal werden 80 patiënten behandeld met een katheter met een groot lumen en 80 met een katheter met een medium lumen. Er werden geen significante verschillen gevonden in percentage van effectieve trombus aspiratie, epicardiale bloeddoorstroming, myocardial blush grade of

electrocardiografische uitkomst tussen de 2 katheters. De grootte van de geaspireerde trombi was eveneens vergelijkbaar.
Deze studie toont aan, dat een groter aspiratie lumen niet direct leidt tot het aspireren van grotere trombi noch in een betere angiografische of elektrocardiografische uitkomst. Dat een groter lumen geen meerwaarde lijkt te hebben, kan verklaard worden door het feit, dat vers gevormde trombi broos en daardoor gemakkelijk te fragmenteren en aspireren zijn. Verder kunnen de betere gebruikseigenschappen van kleinere katheters ook een verklaring zijn van de vergelijkbare resultaten. Bij de evaluatie van alle gepubliceerde data over de verschillende type hulpmiddelen om distale embolisatie te voorkomen, worden de beste resultaten behaald met de meest eenvoudige en gemakkelijk te gebruiken hulpmiddelen.
Verschillende gerandomiseerde studies zijn uitgevoerd, die mechanische trombus aspiratie vergelijken met conventionele PCI, maar met wisselende en minder overtuigende resultaten dan met manuele trombus aspiratie. Echter, er zijn tot op heden geen directe vergelijkingen verricht tussen manuele en mechanische trombus aspiratie. Het is dus momenteel onduidelijk of manuele trombus aspiratie echt superieur is ten opzichte van mechanische trombus aspiratie.

Manuele trombus aspiratie in NSTEMI

In hoofdstuk 9 worden de resultaten van een prospectieve cohort studie gepresenteerd, waarin de haalbaarheid en de veiligheid van trombus aspiratie tijdens PCI voor NSTEMI werden onderzocht. Trombus aspiratie was effectief bij 58 patiënten (83%) en resulteerde in een duidelijke vermindering van de hoeveelheid aanwezige trombus en verbetering van de epicardiale bloeddoorstroming.
Deze studie toont aan, dat trombus aspiratie in de meeste NSTEMI patiënten haalbaar en veilig is. Momenteel wordt de effectiviteit van trombus aspiratie bij patiënten met NSTEMI onderzocht in de Trombus Aspiratie during Percutaneous coronary intervention in Acute non-ST-elevation myocardial infarction Studie (TAPAS II). De TAPAS II zal 540 patiënten met een acuut NSTEMI, die kandidaat zijn voor een spoed PCI, randomiseren naar een behandeling met trombus aspiratie of conventionele PCI. Het primaire eindpunt is de incidentie van myocardial blush grade 3 na PCI.

Direct stenting

In de literatuur wordt gesuggereerd dat in patiënten, die voldoende epicardiale bloeddoorstroming hebben, stent implantatie zonder balloon predilatatie (direct stenting) tot minder distale embolisatie leidt dan stent implantatie met ballon predilatatie. Onduidelijk is, of in deze patiënten groep trombus aspiratie meerwaarde heeft. In hoofdstuk 10 worden STEMI patiënten, die direct stenting ondergingen, vergeleken met patiënten, die voorafgaand aan stent implantatie trombus aspiratie ondergingen. Een totaal van 751 patiënten bleek geschikt voor direct stenting. Direct stenting werd uitgevoerd in 32.6% en trombus aspiratie voorafgaand aan de stent implantatie in 67.4% van de patiënten. Ondanks slechtere angiografische baseline karakteristieken was de groep, die trombus aspiratie voorafgaand aan stent implantatie kreeg, geassocieerd met een aanzienlijke verbetering van het primaire eindpunt myocardial blush grade ten

opzichte van de direct stenting groep. Dit voordeel van trombus aspiratie voorafgaand aan stenting bleef significant na correctie voor bekende prognostische factoren.
Deze bevindingen ondersteunen de hypothese dat, wanneer trombus aanwezig, ook bij normale epicardiale bloeddoorstroming, er nog steeds een hoog risico is op distale embolisatie. Aangezien trombus aspiratie de hoeveelheid trombus vermindert, neemt daarmee ook het risico op distale embolisatie af. Verder wordt gedacht, dat het risico op distale embolisatie het hoogst is tijdens de eerste interventie, ongeacht of dit ballondilatatie of stent implantatie is. Dus ook bij patiënten, die in aanmerking komen voor direct stenting, leidt een PCI strategie die begint, met trombus aspiratie waarschijnlijk tot minder distale embolisatie en een betere microvasculaire reperfusie in vergelijking met enkel direct stenting.

Impact van de interventiecardioloog op microvasculaire reperfusie

In hoofdstuk 11 wordt onderzocht, wat de impact van de interventiecardioloog is op microvasculaire reperfusie. Het primaire eindpunt was de incidentie van optimale microvasculaire reperfusie (myocardial blush grade 3) na de primaire PCI voor STEMI. Er werden in totaal 1071 patiënten geïncludeerd, die een primaire PCI kregen als onderdeel van de TAPAS. Deze PCI's werden verricht door 6 ervaren interventiecardiologen. Alle gebruikte eindpunten waren gescoord door onafhankelijke onderzoekers. Tussen de 6 interventiecardiologen varieerde het percentage van het primaire eindpunt myocardial blush grade 3 tussen 29.2% en 55.5%. Deze associatie tussen microvasculaire reperfusie en interventiecardioloog bleef significant, ook na correctie voor baseline en procedurele verschillen. Er werden geen statistische verschillen gevonden met betrekking tot veiligheidseindpunten.
Deze studie maakt duidelijk, dat zelfs in de gecontroleerde condities van een gerandomiseerde studie een aanzienlijke variatie tussen interventiecardiologen bestaat wat betreft de effectiviteit van primaire PCI. Dit onderzoek ondersteunt het routinematig verzamelen van hoogwaardige datasets om de individuele bekwaamheid en vaardigheden van interventie cardiologen te evalueren en te verbeteren.

APPENDICES

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Curriculum Vitae

Pieter-Jan was born on the 8th of June 1984 in Almelo, the Netherlands. After graduating from the Pius-X College in Almelo in 2002, he studied medicine at the University of Groningen. He performed his internships at the University Medical Center Groningen and Martini Hospital Groningen. During his medical training he performed a semester of research on drug-eluting coronary stents in the Mayo Clinic, Minnesota, United States under the supervision of prof. dr. D.R. Holmes jr. and prof. dr. C.H. Gips. In 2006 he was selected for a MD/PhD project "Strategies to improve myocardial reperfusion after primary PCI" in the department of Cardiology under the supervision of prof. dr. F. Zijlstra and dr. B.J.G.L. de Smet. At present he is a resident in the department of Cardiology at the University Medical Center Groningen.